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The Electrocardiographic Pattern of Hypopotassemia with and without Hypocalcemia

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Detailed analysis of the electrocardiogram in patients with hypopotassemia without hypocalcemia showed that the Q-U interval and its components (Q-oT, Q-aT, Q-T, and Q-aU) have essentially the same duration as in normal subjects for the same heart rate and sex. The typical hypopotassemia pattern is characterized by progressive depression of S-T, lowering and inversion of T and increase of U in left precordial leads. In hypopotassemia with hypocalcemia S-T and Q-T, but not Q-U, are prolonged, causing an increased degree of merging between T and U. Three methods of differentiation between completely merged T and U waves and true T waves of long Q-T duration are given.

IT IS commonly considered that a prolongation of the Q-T duration corrected for the heart rate (Q-Tc) is one of the most characteristic electrocardiographic features of an abnormally low serum potassium (hypopotassemia).[2-10, 12, 14-13, 27-37] As early as 1939 the possibility was mentioned that in some cases of hypopotassemia the wide and notched T wave may include an abnormally high U wave.[17] Other authors also emphasized that in most cases reported as showing a prolonged Q-T duration the U wave was mistakenly considered as the end of the T wave. This concerned diabetics treated with insulin[13] as well as patients with other conditions associated with low serum potassium.[19, 20, 24] Similar

consideration caused McAllen[26] recently to draw the conclusion that a prolongation of the Q-T interval is not commonly associated with a fall in the serum potassium.

The authors considered it important to clarify the divergence of opinion concerning the Q-T duration in hypopotassemia and to determine which are really the most important and characteristic electrocardiographic features associated with this condition. For this purpose the authors decided to apply the methods of accurate measurement of the Q-T duration proper, developed by them in a previous paper,[21] to a larger number of cases of hypopotassemia. These methods included the synchronous registration of many standard and precordial leads together with the heart sounds, which has been carried out only in very few previously published cases. However, even these methods in many cases allowed only an approximate determination of the end of the T wave, and in some cases even an approximate location of this end proved impossible. The authors felt that in such cases measurement of the components of the Q-T duration which can be determined with greater

TABLE 1.—*The Intervals of the Ventricular Complex in Hypopotassemia without Hypocalcemia (Observations 1–26) and with Hypocalcemia (Observations 27–34)* †

Observation No.	Reference No.	Figure No.	Clinical Condition	Sex	Serum K (mEq./L.)	Serum Ca (mEq./L.)	R-R (in 0.01 sec.)	Q-oT (0.01 sec.)	Q-oT as % of normal Q-T	Q-aT (0.01 sec.)	Q-aT as % of normal Q-T	Q-T (0.01 sec.)	Q-Tc in %	Q-aU (0.01 sec.)	Q-aU as % of normal Q-aU	Q-U (0.01 sec.)	Q-U as % of normal QU	Q-2nd sound
1	3	5A	Gastritis, vomiting.	F	2.0	4.6	76	17	46	29	78	36	107	41	87	58	100	—
2	3	8B	Fam. periodic paral.	M	2.9	presum. normal	77	20	60	31	92	36	106	44	96	60	105	—
3	3	2A	Diarrhea. Vomiting.	F	2.2	presum. normal	67	18	53	25?	77?	35	106	37	82	50	96	—
4	9	2 10/12	Treatment of diabetic acidosis.	M	2.1	4.5	72	20	63	26	81	33?	100?	37	82	50	97	—
5	9	3 6/11	Treatment of diabetic acidosis.	F	2.1	4.5	64	16	47	30	88	36	106	—	—	48?	92?	—
6	9	6 11/12	Diarrhea. Uncertain cause.	F	1.0	presum. normal	70	16	47	20'	62	30?	85?	44	96	55	100	—
7	12	183A	Fam. periodic paral.	M	2.5	5.25	68	15	44	23'	75	36	111	43	100	52	100	—
8	14	36A	Diarrhea.	F	2.25	5.2	92	23*	57*	30	75	37	100	43	88	55	89	37
9	17	2	Fam. periodic paral.	M	1.4	5.2	90	19	53	28	78	35	95	44	92	56	92	37
10	26	Case 3	Ulcerative colitis.	F	2.6	5.8	110	20	45	29	73	36?	90?	48	92	66	100	—
11	—	2‡	Intestinal obstruct.	F	2.5	presum. normal	70	17	58	23	68	33	95	44	96	55	100	35
27	37	3MR	Liver cirrhosis.	M	3.7	3.5	60	22	74	28	93	38	126	40	100	49	100	—
28	7	4	Vomiting and K-free infusions.	M	1.3	1.8	68	22	72	29	91	38	118	43	100	53	102	—

* What appeared to be the origin of T may have been the nadir of an initial negative phase of a diphasic T.

† Observation 12–26, see table 3A, observations 1, 2, 3, 4, 6, 7, 12, 13 and table 3B, observations 1, 2, 3, 5, 7. Observation 29–34, see table 3A, observations 5, 8, 10, 11 and B, Observations 6 and 8.

‡ The figure numbers refer to figures of this paper.

accuracy could lead to conclusions regarding the duration of the entire Q-T interval. To facilitate recognition of these components, it was planned to follow the appearance and/or disappearance of the hypopotassemia pattern at very close intervals.

Another aspect which had not been taken into consideration in many of the previous reports was the possibility that other factors concomitant with a low serum potassium were influencing the Q-T duration. The concentration of ionized calcium is among the factors having greatest influence on the Q-T duration. Since disturbances in the concentration of the calcium ion frequently accompany those of potassium metabolism, it seemed imperative to include studies of the blood calcium in the plan of this investigation.

METHOD OF STUDY

For the purpose of detailed study, the ventricular complex of the electrocardiogram was subdivided into a number of components. In order to measure these components accurately, it was necessary to define certain points of the ventricular complex.[22] The beginning of QRS was defined as the earliest point of QRS in synchronous or synchronized leads. The origin of the T wave or the end of the S-T segment was defined as the point most distant from a straight line connecting the S-T junction with the apex of the T wave; it was designated by the symbol "oT." The points "aT" and "aU" represented the apices of the T or U waves respectively. The point "eT" or the end of the T wave was defined as the point where this wave reached the base line; in cases where T did not return to the base line because of partial fusion with the U wave, the notch or kink between the T and U waves was used to determine the approximate end of T.[21] If this point was situated more than 1 mm. from the base line, the accuracy of determination of the end of T was poor; the values obtained in such cases were provided with a question mark. The point "eU" or the end of the U wave could be determined more or less accurately only at low heart rates and with a stable base line. When there was superposition of P on U at high heart rates the measurement was unreliable and the results therefore provided with a question mark. The beginning of the second heart sound (2S) of the phonocardiogram was taken at the first rapid vibrations of this sound.

The points oT, aT, and eT were used for calculation of the intervals in limb leads showing the highest T waves and in chest leads most distant from the transition zone, usually V_4, V_5 and V_6. The points aU and eU were measured in the lead showing the highest voltage of U (usually V_3). In all cases used for this study except one the duration of QRS was normal. In the one case which showed right bundle branch block the difference between the actual duration of QRS and the accepted upper normal limit of 0.10 second was subtracted from all measurements which included the QRS complex, such as Q-oT, Q-aT.

In order to obtain information concerning the normal range of the components described above and their relation to the heart rate, these components were measured in 100 normal persons. The results are presented in detail in a separate paper[22] and summarized in table 4.

In the first part of the present study the electrocardiographic intervals were measured as outlined above in a group of 25 cases of pure hypopotassemia without hypocalcemia. Eighteen of these cases were selected from the literature; only those observations were used which were made when the serum potassium was lower than 3.0 mEq. per liter and when the serum calcium was either found normal by chemical determination or was presumed to be normal because the clinical condition in question is known not to be accompanied by a decrease in the ionized serum calcium. In all cases the serum electrolyte studies were done on the same day as the electrocardiogram. Only cases were included in which a sufficient number of leads was reproduced to enable adequate differentiation between the T and U waves. Among the published cases, only those could be used in which the size of the illustration and the quality of reproduction permitted exact measurements.

In our personal material, all patients admitted to the Bishop DeGoesbriand Hospital in whom hypopotassemia was suspected clinically and all patients in whom the electrocardiogram showed or resembled the hypopotassemia pattern were subjected to detailed studies. The serum potassium and sodium were determined by means of the flame photometer. The serum calcium was determined by the Clark-Collip modification of the Kramer-Tidsall method. The electrocardiogram was registered with the Sanborn direct-writing four-channel electrocardiograph synchronously with the heart sounds; the latter were taken with a magnetic microphone without filter from the aortic region. In some cases it was necessary to change the location of the microphone many times before a satisfactory definition of the second heart sound could be obtained. Our personal material included eight cases. The measurements of this group are presented in table 1 and the results summarized in table 4.

The second group of measurements was performed in 25 cases of pronounced hypocalcemia compiled from the literature. All these cases had a serum calcium below 4 mEq. per liter and complied with the requirements outlined in the preceding paragraphs. They are presented in table 2 and the pertinent results summarized in table 4.

Table 2.—*The Intervals of the Ventricular Complex in Twenty-Five Cases of Hypocalcemia*

Observation No.	Reference No.	Figure No.	Clinical Condition	Sex	Serum Ca (mEq./L.)	R-R (0.01 sec.)	Q-oT (0.01 sec.)	Q-oT as % of normal Q-T	Q-aT (0.01 sec.)	Q-aT as % of normal Q-T	Duration of T-wave (in 0.01 sec.)	Duration of T-wave as % of normal	Q-T (0.01 sec.)	Q-Tc in %	Q-aU (0.01 sec.)	Q-aU as % of normal QaU	Q-U (0.01 sec.)	Q-U as % of normal Q-U	Q-2nd sound (0.01 sec.)
1	1	2 Case 1	Hypoparathyroidism	F	3.9	83	32	85	41	108	16	94	48	137	—	—	—	—	44
2	1	1 22062	Hypoparathyroidism	F	2.7	83	33	88	42	113	18	106	51	146	—	—	—	—	—
3	1	2 Case 2	Hypoparathyroidism	F	3.1	77	—	—	32	89	—	—	44	130	—	—	—	—	42
4	1	2 Case 3	Hypoparathyroidism	F	2.55	80	29	81	41	110	19	111	48	140	—	—	—	—	—
5	1	2 24561	Hypoparathyroidism	F	3.45	100	32	81	43	108	20	111	52	146	—	—	—	—	45
6	1	1 24559	Hypoparathyroidism	F	3.85	78	24	63	34	93	17	103	41	120	48	100	57	98	—
7	1	2 Case 4	Nephritis. Uremia	M	3.0	60	32	105	38?	126?	11?	85?	43?	142?	—	—	—	—	35
8	1	2 Case 5	Nephritis. Uremia	M	2.4	84	40*	112	48?	136?	—	—	52?	146?	—	—	—	—	37
9	1	2 Case 6	Nephritis. Uremia	M	3.15	104	38	102	47?	115?	18?	103?	56?	145?	—	—	—	—	44
10	9	1	Hypoparathyroidism	M	2.2	86	40	113	48	135	—	—	60	170	—	—	—	—	—
11	18	275b	Hypoparathyroidism	M	2.15	88	34	94	43	117	14	83	48	133	50	104	64	107	—
12	25	1d	Hypoparathyroidism	F	2.9	60	28	86	37	117	19	136	47	155	—	—	—	—	—
13	37	2 4/27	Uremia	F	2.0	84	35	91	40	105	14	83	49	138	55?	110?	64?	107?	—
14	37	2 5/1	Uremia		2.95	100	33	78	38	93	16	90	49	128	54?	104?	70?	110?	—
15	37	3 L.T.	Uremia	M	2.35	80	28	82	39	112	17	100	45	126	50?	106?	62?	108?	—
16	37	4 M.M.	Glomerulonephritis	M	2.8	70	24	74	32	98	16	100	40	123	—	—	—	—	—
17	37	5 E.F.	Hypoparathyroidism	F	2.2	78	26	70	33	88	14	85	40	115	40?	84?	46?	80?	—
18	14	54	Sprue	F	2.9	86	36	94	42	110	14	78	50	140	54		62	100	47
19	23	256	Chronic nephritis	F	2.2	87	31	78	39	103	15	88	46	128	54	110	65	107	44
20	25	1b	Hypoparathyroidism	F	2.8	92	31	82	39	103	17	100	48	125	—	—	—	—	—
21	25	2a	Hypoparathyroidism	F	2.7	100	32	82	41	105	16	91	48	120	—	—	—	—	—
22	25	5a	Hypoparathyroidism	F	2.4	90	38	102	48	129	17	100	55	145	—	—	—	—	49
23	15	88a	Hypoparathyroidism	F	—	83	31	86	37	103	13	73	44	121	53?	108?	—	—	43
24	15	89a	Tetany		2.25	71	32	94	39	115	15	98	47	140	48?	104?	—	—	—
25	15	91a	Tetany	F	—	63	30	94	36	112	12	89	42	132	—	—	—	—	39

* What appeared to be the origin of T may have been the nadir of an initial negative phase of a diphasic T.

The third series of measurements was carried out in eight cases of hypopotassemia with concomitant hypocalcemia. These cases had a serum potassium lower than 3.7 mEq. per liter and a serum calcium lower than 4.2 mEq. per liter. Only six published cases and two personal cases met the requirements of this study. The measurements in these cases are included in tables 1 (cases 26–27), 3 A (cases 5, 8, 10 and 11) and 3 B (cases 6 and 8). The results are summarized in table 4. In one additional case, which was included for the purpose of comparison, hypercalcemia was present in addition to hypopotassemia (table 3 B, case 4).

The fourth series of measurements concerned cases of hypopotassemia in which only one of the serum electrolytes (potassium or calcium) was altered while the other remained unchanged. In 13 of these the measurements were made in illustrations published by other authors. These include 10 observations in which potassium was given until the serum potassium level became normal, and three observations in which calcium was given. Our personal material consists of five cases in which potassium was given, one case in which the serum potassium changed spontaneously, and two patients in whom calcium was injected intravenously.

The RS-T Segment and the Q-oT Interval

In our studies in normal subjects[22] we found that the duration of the interval from the beginning of QRS to origin of the T wave (Q-oT interval) showed the same dependence on the heart rate and sex as the Q-T interval. Expressed as a percentage of the Q-T interval expected for the heart rate, it ranged between 49 per cent and 63 per cent, averaging 56 per cent (table 4) independently of heart rate and sex. The normal limits, therefore, could be considerably reduced if the Q-oT interval in all cases was expressed as a percentage of Q-T rather than as an absolute value. As in many cases the Q-T interval could not be determined accurately, the Q-oT interval was expressed as a percentage of the normal Q-T interval expected for the heart rate. We designated this value the "corrected Q-oT interval" or "Q-oTc." In our group of hypocalcemia cases Q-oTc exceeded the normal upper limit of 63 per cent in all cases, reaching values as high as 113 per cent; the average was 88 per cent, which was 58 per cent higher than the normal average (tables 2 and 4).

Of the 25 cases of hypopotassemia included in table 1, eight showed a horizontal or ascending course of the S-T segment in leads with upright T waves (figs. 1, 4A, 7A). In these cases the origin of the T wave and the Q-oT duration could be identified and measured without difficulty. In cases showing a more fully developed hypopotassemia pattern the S-T segment begins to slope downward, terminating in a diphasic (negative-positive) T wave in the left precordial leads. If the Q-oT interval is measured in these leads, pseudo-short values would be obtained. In such cases the Q-oT interval was measured in those leads which showed a fully monophasic upright or inverted T wave. In figures 2 and 6a–j, for instance, leads II, aV_F, aV_R, and V_4, V_5 and V_6 have diphasic T waves, but lead aV_L has a monophasic upright wave; the Q-oT duration was accordingly measured in these leads. In figure 3A leads I, II, III and V_4 have diphasic T waves, while leads V_1 and V_2 have monophasic upright waves and lead V_6 has a monophasic inverted T wave; the Q-oT interval was accordingly measured in the latter leads.

In four of the 25 cases a monophasic upright or inverted T wave could not be found in any of the recorded leads; as the RS-T segment in these cases had a straight downward course, the origin of the T wave, strictly speaking, could not be determined. In such cases it was felt that the nadir of the initial negative phase of T represented the nearest approach to the origin of T, and this nadir was therefore measured instead of the point oT (figs. 6b and 8A). The value of the Q-oT duration measured in this way was slightly greater than the true Q-oT value, and therefore was designated with an asterisk in the table.

In a few cases of hypopotassemia the sudden increase in the slope of the S-T segment corresponding to the origin of the T wave was preceded by an additional kink or change in slope, which could be mistaken for a very early origin of the T wave. This pattern could be seen in figure 1 of reference 36a, figure 4c–d of reference 26 and is well illustrated by leads I and V_4, V_5 and V_6 of figure 6c. These leads may convey the impression that there is a very short descending S-T segment followed by an early upright T wave. Comparison with the same leads taken previously or following the tracings displaying this pattern (figs. 6a, b and d) shows, however, that this segment corresponds in time to a slurred terminal portion of the QRS group. Accordingly the tracing should be interpreted as showing an ascending S-T segment followed by an inverted first phase of a diphasic T wave. It is of interest that all cases showing this pattern had serum potassium levels lower than 2 mEq. per liter. In figure 6 the purest pattern of a monophasic positive T was found in lead aV_L, and the Q-oT interval was accordingly measured in this lead.

As can be seen in table 4, the corrected Q-oT interval is normal in hypopotassemia,

TABLE 3.—*The Effect of Changes in the Concentration of Serum K or Ca on the Intervals of the Ventricular Complex in Hypopotassemia.*

A. Observations from Literature

Observation No.	Reference No.	Figure No.	Short Description of the Case	Serum K (mEq./L.)	Serum Ca (mEq./L.)	R-R (0.01 sec.)	Q-oT (0.01 sec.)	Q-oT as % of normal Q-T	Q-T (0.01 sec.)	Q-T as % of normal Q-T	Q-T (0.01 sec.)	Q-Tc in %	Q-uU (0.01 sec.)	Q-uU as % of normal Q-uU	Q-U (0.01 sec.)	Q-U as % of normal Q-U	Q-U expressed as Q-Tc in %
1	2	1A	Cholecystitis, vomiting.	2.85	normal	122	24	57	40	95	48?	115	57	108	66	100	160
		1C	After K administration.	4.08	normal	100	28	74	38	100	48	115	53	102	73	114	
2	2	2A	Pyloric obstruction and vomiting.	2.7	4.9	67	22	67	33	103	37	113	45	100	50	94	155
		2C	After K administration.	4.3	4.8	70	24	75	32	100	36	110	46	100	52	95	
3	2	4B	Ruptured duodenal ulcer and K-free infusions.	2.3	normal	72	19	57	27	82	34	104	41	90	48	86	146
		4F	After K administration (food)	4.5	4.7	72	17	52	26	78	38	115	42	92	53	94	
4	9	4 3/1	Diabetic coma treated with K-free infusions.	1.75	4.8	82	20*	57	25	72	37	100	42	86	50	88	145
		4 3/3	After K administration.	3.5	4.8	70	24	75	27	83	40	113	42?	91?	—	—	
5	9	5 4/5	Over - treatment with DOCA and low K diet.	1.35	3.95	130	24	54	36'	82	50	115	62	119	74	114	170
		5 5/2	DOCA discontinued.	4.0	4.9	90	24	66			42	115	—	—	64	106	
6	9	2 10/9	Diabetic coma treated with K-free infusions.	2.15	4.5	60	18*	60	20	66	30	100	34	90	46?	100%	150
		2 10/8	After K administration.	5.25	4.5	90	23	64	30	83	38	104	44	90	—	—	
7	27	2 Day 2	Diabetic acidosis.	2.77	4.4	70	18	56	25	78	30	92	36	102	46		142
		2 Day 6	Recovery.	4.31	4.75	90	20	55	30	83	36	98	—	—	—		
8	33	5 0 hr.	Chronic nephritis and uremia.	2.7	2.3	84	34	95	43	120	46	135	56	114	64	107	180
		6½ hr.	After K administration.	4.9	2.3	80	35	103	43	125	48	139	56	116	68	116	
9	33	5 6½ hr.	Chronic nephritis and uremia after K administr.	4.9	2.3	80	35	103	43	125	48	139	56	116	68	116	
		5 7½ hr.	After Ca administration.	4.4	3.8	114	32	78	40	98	50	110	59	113	74	113	
10	8	5 0 hrs.	Sprue. Diarrhea & tetany.	2.8	3.15	68	22*	69		—	36?	112?	42	100	50	98	155
		5 2 hrs.	After Ca administration.	2.6	4.7	68	16*	50		—	30	94	42	93	50	93	155
11	8	2 5 day	Diarrhea.	2.6	2.25	76	22*	65		—	40	120	45	94	54	93	160
		2 32 day	After Ca administration.	2.6	3.85	80	16*	47		—	35?	102?	45	98	57	98	170
12	36	1A	Addison's Disease.	7.9	4.45	93	24	65	28	76	37	100	—	—	50	96	
		1B	Treated with DOCA.	4.0	5.75	72	21	65	28	82	36	110	43	98	50	96	
		1C	Over-treated with DOCA.	2.1	4.45	88	23	64	31	86	36	100	51?	106?	55	93	
13	34	1B	Fam. periodic paralysis.	2.75	5.3	58	16?	53?	—	—	—	—	39	100	—	—	—
		1C	After K administration.	2.75		67	19	59	24	75		105		93	12?	104?	—
		1F	After K administration.	4.5	5.85	76	21	62	26	76	36	110	44	100	58	106	—

B. Personal Cases

Observation No.	Patient	Date	Short Description of the Case	Serum K (mEq./L.)	Serum Ca (mEq./L.)	R-R (0.01 sec.)	Q-oT (0.01 sec.)	Q-oT as % of normal Q-T	Q-aT (0.01 sec.)	Q-aT as % of normal Q-T	Q-T (0.01 sec.)	Q-Tc in %	Q-aU (0.01 sec.)	Q-aU as % of normal Q-aU	Q-U (0.01 sec.)	Q-U as % of normal Q-U	Q-2nd sound
1	Bus. 23♀	3/7 8 p.m.	Vomiting in pregnancy	2.7		70	20	58	28	82	38	108	45	98	53	96	37
		3/7 9 p.m.	After infusion 30 mEq. K	3.13		69	20	58	28	82	37	106	45	98	52	95	38
2	Wal. 80♂	5/7	Sigmoid car.; diarrhea.	2.1	5.25	63	23	74	28	90	33?	105?	38	98	49	103	28
		5/8	After infusion 60 mEq. K.	—	—	62	23	74	28	90	33?	105?	40	100	48	102	32
		5/9	After infus. 60 mEq. K. & whole blood.	3.59	—	65	23	72	29	90	40?	128?	42?	102?	50	100	36
		56/10	After infusion 60 mEq. K.	—	—	59	22	73	28	94	36	120	—	—	—	—	28
3	War. 63♂	5/6	Intestinal obstruction; vomiting.	2.4	4.5	64	19	61	23'	74'	28?	90?	33	81	44	93	28
		5/7	After 40 mEq. K & 1000 cc. whole blood.	2.8	4.2	52	17	60	21'	74'	29	102	33	100	42	100	30
		5/8	After infusion 145 mEq. K.	3.1	—	57	18	60	22'	73'	29?	97?	34	92	44	100	27
		5/10	After infusions of K.	—	—	48	16	58	22	80	28	101	31	100	42?	—	25
4	DeC. 56♀	2/11 9:00	Reticulum cell sarcoma; cachexia, vomiting.	3.2	6.7	49	14	50	18'	64'	28?	100?	39?	100?	—	—	34
		9:45	After infusion 15 mEq. K.	—	—	50	15	54	18	64	28?	100?	36?	93?	—	—	32
		10:45	After infusion 40 mEq. K.	—	—	56	17	59	21	73	29	100	40?	98?	—	—	36
		11:05	After infusion 45 mEq. K.	—	—	78	22	58	28	73	32	94	43	90	58	100	36
5	P.R. 23♀	3/8 3 a.m.	Diarrhea	1.5	—	64	16	48	25	76	29	88	38	90	50	96	—
		3/8 10:45	After 15 mEq. K.	—	—	45	16*	57*	21	75	25	90	31	92	—	—	22
		3/9 10a.m.	After 1000 cc. whole blood.	—	—	64	16	48	21	64	30?	91?	42	98	48	92	28
		11:45	After infusion 5 mEq. K.	—	—	64	17	52	24	73	31?	94?	40	94	49	94	27
		1 p.m.	After infusion 20 mEq. K.	—	—	64	19	58	27	82	32	97	40	94	49	94	31
		6 p.m.	After infusion 80 mEq. K.	—	—	51	19	63	27	91	34	107	—	—	—	—	29
		7:30	After infusion 145 mEq. K.	—	—	52	16*	54*	25	84	35	110	—	—	—	—	32
		3/10 10a.m.	After recovery.	2.9	4.7	52	19	63	26	87	33	105	—	—	—	—	32
		3/16		4.0	—	42	12	45	20	74	26	96	—	—	—	—	28
6	Hal. 47♀	12/4	Idiopathic steatorrhea.	3.0	4.2	70	25	74	31	91	39	120	42	92	49	89	35
		12/4	5 min. p. 10 cc. 10% CaCl₂ I.V.	—	—	98	19	50	25	65	37	95	49	96	58	93	34
7	Cl. 56♂	11/7	Colon car., colostomy, diarrhea.	2.7	4.9	56	20	69	29?	100?	—	—	—	—	—	—	30
		11/7	4 min. after 20 cc. 10% Ca glucose I.V.	—	—	56	17	58	28?	96?	—	—	—	—	—	—	29
8	Aus. 37♀	3/25	Uremia in bladder car.	5.8	4.4	61	20	61	27	82	34	105	40	95	52?	102?	35
		4/21		3.0	3.15	61	26	81	35	109	41	130	41?	98?	50	98	33

* What appeared to be the origin of T may have been the nadir of an initial negative phase of T.

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TABLE 4.—*Summary of the Most Important Values for the Duration of the Components of Ventricular Activity in Relation to the Serum Potassium and Calcium*

Condition	No. of observations	Mean serum concentration (mEq./L.)		Q-oTc (as % of normal Q-T)			Q-aTc (as % of normal Q-T)			Q-Tc (as % of normal Q-T)			Q-aUc (as % of normal Q-aU)			Q-Uc (as % of normal Q-U)			aT-2nd sound (0.01 sec.)			T-2nd sound (0.01 sec.)			aU-2nd sound (0.01 sec.)		
		K	Ca	min.	aver.	max.	min.	aver.	max.	min.	aver.	max.	min.	aver.	max.	min.	aver.	max.	min.	aver.	max.	min.	aver.	max.	min.	aver.	max.
Normals	100	4.8	5.1	49	56	63	62	78	92	92	101	111	90	100	110	92	100	116	6	8.5	12	-2	0.7	3	-14	-9	-4
Hypocalcemia (serum Ca below 4.0 mEq./L.)	25	—	2.7	63	88	113	88	110	135	115	135	146	84	103§	110	80	102†	110	-1	11.6*	10	-15	-5.7*	-1	-19	-10.5*	-3
Deviation from normal in %			-47		+58			+41			+34			+3			+2										
Hypopotassemia (serum K below 3.0 mEq./L.)	26	2.3	—	44	57	74	64	80	103	92	103	115	82	94	106	86	96	105	0	7	12	-5	-1†	2	-14	-8†	-3
Deviation from normal in %		-53			+2			+3			+3			-6			-4										
Hypopotassemia with hypocalcemia (serum K below 3.7 mEq./L. & Serum Ca below 4.2 mEq./L.)	8	2.5	3.1	54	73	95	82	100	120	112	123	135	92	103	119	89	100	114		2‡			-6‡			-7‡	
Deviation from normal in %		-48	-39		+30			+29			+22			+3			0										
Hypopotassemia with hypercalcemia	1	3.2	6.7		50			64			100?			100?			—			16			6?			-5?	
Deviation from normal in %		-34	+31		-11			-18																			

* Based on 11 cases only.
† Based on 8 cases only.
‡ Based on 2 cases only.
§ Based on 9 cases only.
‖ Based on 19 cases in which Q-T could be measured accurately. See discussion.

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but increased when hypopotassemia is accompanied by hypocalcemia and decreased when it is accompanied by hypercalcemia. In the 15 cases of hypopotassemia in which potassium was given (table 3), the Q-oTc duration showed an average increase of 1.6 per cent, the changes ranging from a decrease of 3 per cent to an increase of 9 per cent.
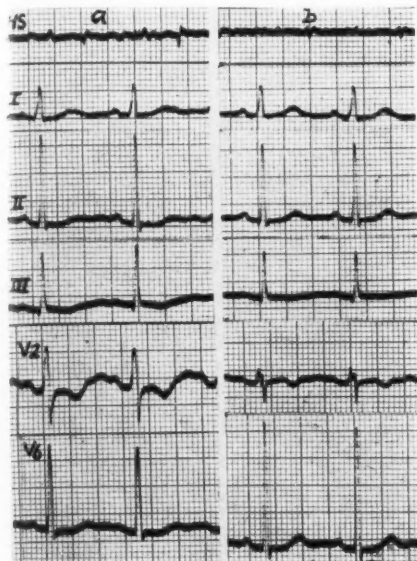
Fig. 1. Observation 1, table 3B. Severe vomiting in pregnancy. Heart sounds (HS) synchronous with leads I, II and III, and lead V_2 synchronous with lead V_6.

(a) Serum potassium = 2.7 mEq. per liter. Serum sodium = 137.2 mEq. per liter. Leads II and V_6 show characteristic depression and "sagging" of S-T, moderate depression of T and moderate elevation of U. (b) Serum potassium = 3.13 mEq. per liter, serum sodium = 138.1 mEq. per liter. After infusion of potassium. Normalization of the electrocardiogram.

These are insignificant changes, so that the conclusion can be made that the Q-oT duration is not influenced by potassium.

In case 5 of table 3 B (fig. 6) infusion of potassium over a period of six hours caused an increase of Q-oTc from 48 per cent to 63 per cent (a total of 15 per cent). During this period of time the patient continued to have severe diarrhea, so that it is probable that the serum calcium became progressively lower toward the end of the infusion. This

might explain the exceptionally large increase of the Q-oTc duration in this case. In all except two cases, administration of potassium caused the S-T segment in the left ventricular epicardial leads to change from a descending "sagging" course to a horizontal and finally to a normally ascending course (figs. 1, 3, 6, 8B and 9). In the exceptions (figs. 4 and 6) the S-T segment became more descending in spite of continuing potassium administration. In figure 6 this change was transient and could have
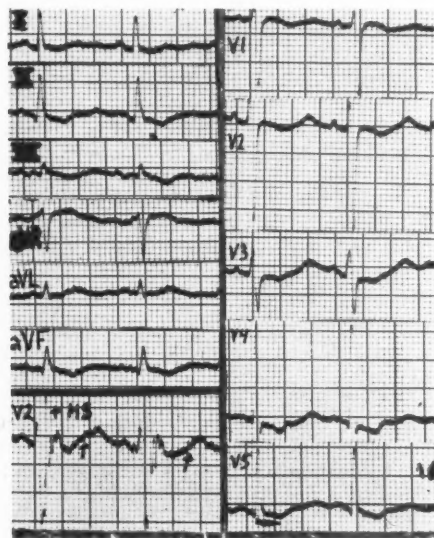
Fig. 2. Observation 11, table 1: Intestinal malignancy with diarrhea; hypopotassemia after infusion of normal saline (serum potassium = 2.5 mEq. per liter). Nonsynchronous standard and unipolar limb leads and unipolar precordial leads. In the tracing marked V_2 + HS, the lead V_2 was taken through a magnetic microphone in the region of the great vessels. The first heart sound is partly superimposed on the S wave; the second heart sound (marked with arrows) is superimposed on the kink between a negative T wave and an elevated positive U wave. Diphasic (minus-plus) T waves in leads II and V_2–V_6, monophasic upright T waves in aV_L. U waves elevated in all precordial leads.

been caused by increased depletion of potassium and/or calcium due to persistent diarrhea. In figure 4 the serum potassium continued to rise, but the serum calcium became lower. These two cases will be discussed in detail later.

In the five cases of hypopotassemia in which calcium was injected, the Q-oTc duration decreased from 11 to 35 per cent (on the average 22 per cent). The course of the S-T

segment was not significantly changed (figs. 7 and 8).
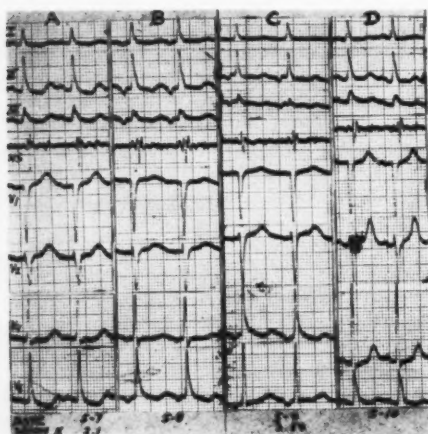
FIG. 3. Observation 2, table 3B. Hypopotassemia due to persistent diarrhea in sigmoid carcinoma and terminal intestinal obstruction with vomiting. Heart sounds (HS) synchronous with leads I, II and III.

(A) Serum potassium = 2.1, sodium = 129, calcium = 5.25, chloride = 81, and carbon dioxide = 31.2 mEq. per liter. Nonprotein nitrogen 59 mg. per 100 cc. Depression and downward course of S-T; diphasic (minus-plus) T waves partly fused with elevated upright U waves in leads I, II and III and V_4. Negative T in V_6. Upright T waves completely fused with elevated U waves in leads V_1 and V_2. The apex of the T plus U complex is formed by the apex of U. (B) After infusion of potassium. Upper nodal rhythm; amplitude of U diminished. (C) Serum potassium = 3.59, sodium = 141.8 mEq. per liter. After further administration of potassium. Nodal rhythm persists but T is more positive. (D) After further infusion of potassium. Restitution of sinus rhythm. The T waves are now upright in all leads except V_6; the apex of the T plus U complex is formed by the apex of T.

The T Wave and the Q-aT and Q-T Durations

In our studies in 100 normal persons[22] we found that the duration from the beginning of QRS to the end of T (Q-T duration) showed a dependence on the heart rate according to the empiric curve derived by one of us from 1000 personal and 3000 published normal cases.[19, 20] This curve is situated approximately midway between the logarithmic curve of Ashman and the square-root formula of Bazzett.[20] The values for females were, however, about 7 per cent above this curve. In order to obtain the
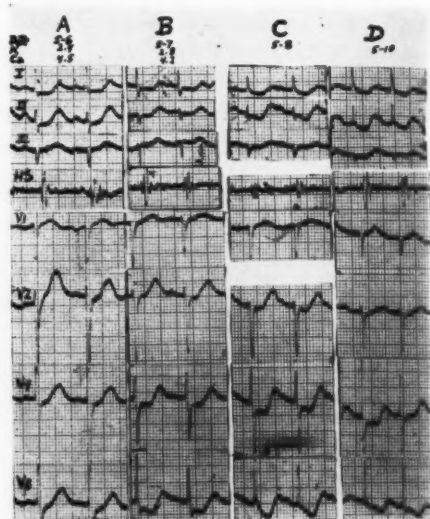
FIG. 4. Observation 3, table 3B. Carcinoma of terminal colon. Intestinal obstruction, vomiting of four days' duration. The heart sounds (HS) are synchronous with leads I, II and III in A and B, with V_1 in C, and with V_1, V_2 and V_6 in D.

(A) Serum potassium = 2.5, sodium = 116, calcium = 4.5, chloride = 77.7, and carbon dioxide = 13.1 mEq. per liter. Nonprotein nitrogen 105 mg. per 100 cc. Depression of S-T; T and U are almost completely merged; a kink between a diphasic T wave and a high positive U wave appears to be present in lead V_4. The apex in all leads except V_1 is formed by the U wave. (B) After infusions of potassium and blood transfusions. Serum potassium = 2.8, calcium = 4.2 mEq. per liter. S-T depression slightly less pronounced, amplitude of U wave diminished. (C) After further infusions of fluids containing potassium. Continuing diarrhea. Serum potassium = 3.1, sodium = 139.2, carbon dioxide = 13.9 mEq. per liter. Nonprotein nitrogen 120 mg. per 100 cc. Further decrease of amplitude of U, S-T segment more depressed and T wave more inverted. (D) After infusions of potassium. Further decrease of the amplitude of U, U partly merged with P, P-R interval prolonged; apex formed by positive T wave in leads V_1 and V_2 and by negative T wave in leads II and V_6; T appears to be diphasic and partly merged with U in leads I, III and V_4.

predicted normal Q-T duration for the heart rate, the values obtained from this curve were used without modification for males but 7 per cent was added in the case of females. The

actual Q-T duration was expressed as a percentage of the predicted normal Q-T duration for the heart rate and sex. The duration from the beginning of QRS to the apex of the T wave (Q-aT duration) was found to show the same dependence on the heart rate and sex as the entire Q-T duration; when it was expressed as a percentage of the predicted Q-T duration for the heart rate and sex, it became practically independent of these factors. It ranged from 62 per cent to 92 per cent with an average of 78 per cent.

As can be seen in table 4, the average corrected Q-T duration in hypocalcemia was 35 per cent longer while the corrected Q-aT duration was 41 per cent longer than in normal persons. The duration of the T wave, expressed as a percentage of this duration in normal persons for a given heart rate, ranged from 73 per cent to 136 per cent of normal, but the average was 100 per cent. This confirms the findings of other authors[9, 11, 24, 37]* that the duration of T is not increased in hypocalcemia and the prolongation of Q-Tc is due entirely to a lengthening of the S-T segment.

Because of the profound changes which the T wave undergoes in hypopotassemia, the method of measurement of the apex and end of this wave requires a special discussion. In those cases of hypopotassemia where the T wave still retains its normal direction, the identification of the apex of T presents no difficulties (fig. 1). The difficulties arise when the T wave becomes either isoelectric or diphasic. In the great majority of cases one or more leads can be found in which the T wave is monophasic (upright or inverted). In figures 2 and 6, lead aV$_L$ shows a monophasic upright T, while in figure 3A lead V$_6$ shows monophasic inverted T waves; these leads were accordingly used to measure the apex of T. In four cases from the literature and in one of our own cases (fig. 4B–C) all of the registered leads showed diphasic T waves. In these cases the apex of the first negative phase of T was used instead of the true apex of T; and in the tables the values of Q-aT obtained in this way were designated by a "prime" (') sign. In one case the T wave was nearly isoelectric in all registered leads, so that its apex could not be determined accurately; in this case the values were provided with a question mark.

As mentioned under "Methods," accurate determination of the end of the T wave and therefore of the Q-T duration could be made only in cases

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* Other references may be found in reference 20.

where the T wave retained its normal configuration and showed no appreciable merging with the U wave (fig. 1a). This occurred only in cases of mild hypopotassemia (fig. 1). With further development of the hypopotassemia pattern, the T wave becomes lower and the U wave becomes higher. This causes the notch between the T and U to become displaced further from the base line and to become less accurate as an indication of the end of T. In these cases, as well as in those in which the notch was in-
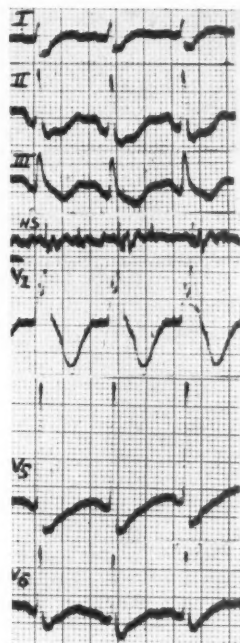

FIG. 5. Observation 7, table 3B. Rectovesical fistula. Acute ulcerative colitis. Diarrhea. Serum potassium = 2.7, sodium = 133, calcium = 4.9 mEq. per liter. Hypopotassemia pattern modified by right bundle branch block. See text, page 824. Heart sounds (HS) synchronous with the precordial leads.

distinct, the values of Q-T were provided with a question mark (fig. 4, leads V$_4$, V$_5$ and V$_6$). When the T wave becomes diphasic (negative-positive), there is usually a definite notch between the terminal phase of T and the U wave (fig. 2, lead V$_4$); if this notch is indistinct, the measurements are again provided with a question mark (figs. 4C, 6c, d). When the T wave becomes negative, its ascending branch usually makes a definite kink with the U wave, but sometimes this kink was indistinct; under these circumstances the Q-T duration was again provided with a question mark (fig. 3A).
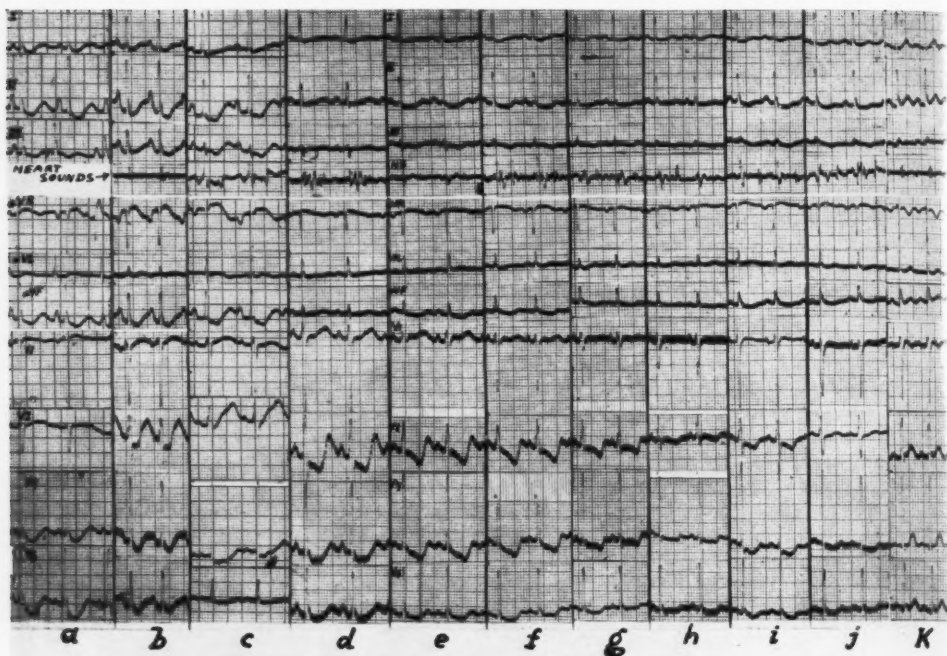
Fig. 6. Observation 5, table 3B. Severe acute diarrhea following a long period of treatment for burns covering 40 per cent of body area. The heart sounds (HS) are synchronous with leads I, II and III in b and in d through k; they are superimposed on lead V₃ in a and c.

(a) About 20 minutes after manifestations of tetany, treated with 15 cc. intravenous 10 per cent calcium gluconate. Elevation of P, slurred terminal portion of R. Depressed, sagging S-T and diphasic (minus-plus) T waves merged with elevated U waves in leads I, II and III, aV_F and V₄, V₅ and V₆. Upright T waves in aV_L and V₁ and V₂. In lead III and aV_R auricular premature beats with aberrant intraventricular conduction. (b) After intravenous infusion of 15 mEq. potassium and 0.5 Gm. calcium gluconate. Increased depression of P-R and S-T. U waves merged with T waves. (c) On the following day. Diarrhea persists. After 1 liter whole blood. Serum potassium = 1.5, sodium = 1.29, chloride = 66.2, carbon dioxide = 43 mEq. per liter. Nonprotein nitrogen 115 mg. per 100 cc. Leads I and V₄ show apparent kink in S-T segment due to end of slurred QRS. (d) After infusion of 5 mEq. potassium phosphate in saline. Complete infusion of T and U in lead II; U is lower. (e, f, and g) After infusion of 20, 50 and 80 mEq. of potassium, respectively. The U wave becomes progressively smaller while the negative phase of T becomes progressively less deep. (h) After infusion of 145 mEq. potassium phosphate in saline. Positive T wave components with prolonged S-T segments are now visible in most of the leads. (i) On the following day. Diarrhea continues with less intensity. Serum potassium = 2.9, sodium = 138.6, calcium = 4.7, chlorides = 106, and carbon dioxide = 20.4, mEq. per liter, pH 7.48. Nonprotein nitrogen 55 mg. per 100 cc. Depression of S-T is again more pronounced. (j) After infusion of 18 mEq. potassium phosphate. S-T less depressed, T more positive. (k) Six days later, after recovery from diarrhea. Serum potassium = 4.0, sodium = 140.4, chlorides = 108, carbon dioxide = 24.6 mEq. per liter. Nonprotein nitrogen 29 mg. per 100 cc. The electrocardiogram is now normal.

It is apparent from table 4 that the average corrected Q-T and Q-aT duration in "pure" hypopotassemia does not deviate significantly from the values in normal persons. When hypopotassemia is accompanied by hypocalcemia, both these values are significantly prolonged, while when it is accompanied by hypercalcemia, they are significantly shorter than in normal persons. In the 15 cases of hypopotassemia in which potassium was given (table 3), Q-aTc showed an average increase of 4.6 per cent, the changes ranging from a

decrease of 4 per cent to an increase of 17 per cent. Q-Tc showed an average increase of 4.9 per cent, the changes ranging from a decrease of 6 per cent to an increase of 15 per cent. The changes are probably not significant and can be explained in part by the fact that the more nearly normal configuration of the T waves after administration of potassium allowed more accurate determination of the Q-aT and Q-T duration (page 811). In all cases the T wave showed a tendency toward positivity in the left ventricular epicardial leads. In other words, when it was originally low positive it became higher positive; when it was diphasic, the voltage of the negative phase decreased while that of the positive phase increased; when it was negative, its voltage decreased.

In the five cases of hypopotassemia in which calcium was injected, Q-aTc could be measured accurately only in two cases; these showed a decrease of 26 per cent and 27 per cent respectively. Q-Tc could be determined only in four cases, and in these it showed a decrease ranging from 18 per cent to 29 per cent and averaging 25 per cent. The amplitude and configuration of T were very little influenced.

The U Wave and the Q-aU and Q-U Durations

In our study of 100 normal cases[22] we found that the duration from the beginning of QRS to the apex of the U wave (Q-aU duration) became longer with a falling heart rate. The duration from the end of T to the apex of U remained approximately constant (0.10 second) at all heart rates. The interval from the beginning of QRS to the end of U (Q-U interval) showed a much greater increase with falling heart rate than Q-aU. Women had longer Q-aU and Q-U intervals than men at all heart rates. In this paper we have expressed the observed Q-aU and Q-U intervals as a percentage of the normal values for the heart rate and sex found in our previous study. These percentages are designated as the "corrected Q-aU and Q-U intervals" or Q-aUc and Q-Uc.

Of the 25 cases of hypocalcemia (tables 2 and 4) no U waves were visible in the registered leads in two thirds of the cases. In the seven

cases where U was visible, the apex of U could be measured accurately only in three cases while the end of U could be measured accurately only in four cases; in the other cases the results of the measurements were provided with a question mark. In the cases where it
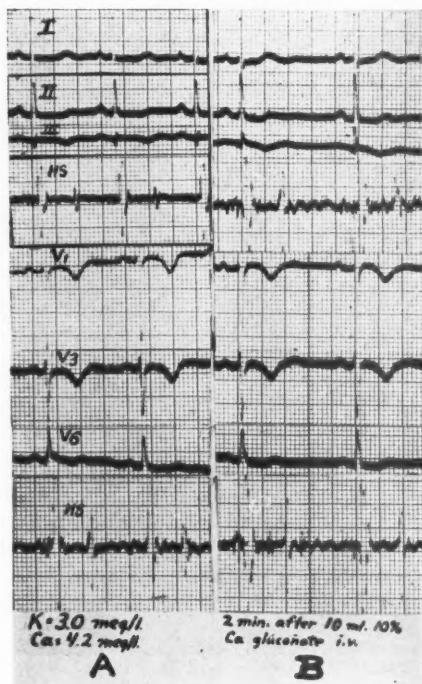
Fig. 7. Observation 6, table 3B. Idiopathic steatorrhea with osteomalacia of five years' duration. Heart sounds (HS) synchronous with the limb and precordial leads. (A) Serum potassium = 3.0, sodium = 142, calcium = 4.2, chloride = 114.5, carbon dioxide = 20 mEq. per liter. Total proteins = 5.7 Gm. per 100 cc., inorganic phosphorus = 1.8 mg. per 100 cc. Depressed, prolonged S-T segment in leads I, II and V_6. T waves positive in lead I, diphasic in leads II and V_6, negative in III and V_1, V_2 and V_3, and merged with U waves. (B) Following intravenous calcium administration. Shortening of the S-T and Q-T duration; separation of T from U.

could be determined accurately, Q-aU ranged from 100 per cent to 110 per cent and averaged 104.4 per cent of normal; if the cases with question marks are included, the lower range becomes 84 per cent and the average 103.3 per cent. The distance between the end of T and the apex of U ranged from 0.02 to 0.08 second

with an average of 0.056 second in the cases without question mark, and from 0.0 to 0.9 second with an average of 0.05 second in the entire material. The average value for this distance is accordingly less than the lowest value observed in normal persons, namely, 0.06 second. We see, therefore, that the apex of U in hypocalcemia occurs approximately at the expected normal time, and that its distance from the end of T becomes shorter because of the prolonged Q-T interval. It is probable also that the reason why the U wave could not be

the apex but also the end of U appear at the expected normal time in hypocalcemia.

In our cases of hypopotassemia without hypocalcemia (tables 1 and 4) the U waves were always of normal amplitude or elevated, and the Q-aU and Q-U intervals could be measured accurately in nearly all cases. The Q-aU interval averaged 94 per cent, while the Q-U interval averaged 96 per cent of normal. This means that in hypopotassemia the apex as well as the end of the U wave appears slightly earlier than normally. As the end of T
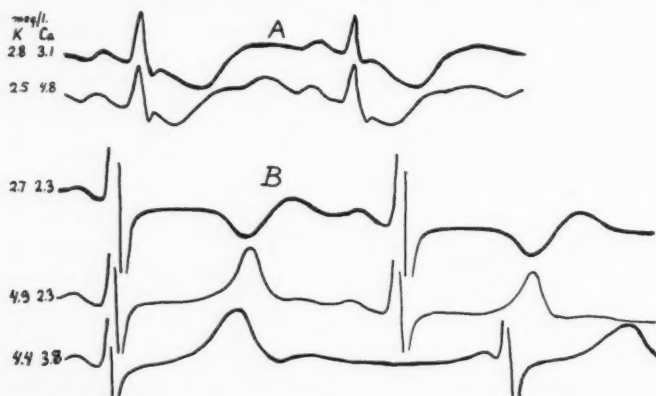
FIG. 8. (A) Observation 10, table 3A. Lead II, retraced from figure 5 of Engel, Martin and Taylor.[8] Sprue with diarrhea and tetany, before and after administration of calcium. Depressed, sagging S-T segment, diphasic (minus-plus) T waves and elevated U waves, merged with T. After calcium, shortening of S-T and Q-T and separation of T from U. (B) Observations 8 and 9 of table 3A. Lead V₅, retraced from figure 5 of Reynolds, Martin and Homann.[33] Chronic nephritis and uremia with hypocalcemia and hypopotassemia. Depressed, prolonged S-T segment, negative T wave merged with elevated U wave. After administration of potassium (second row) the depression of S-T disappears, the T wave becomes upright and the U wave lower, but the duration of all components is unchanged. After administration of calcium (third row), shortening of S-T and Q-T and separation of T from U.

seen in the majority of the cases was that it was masked by the end of the T wave. When we determined the relation of the expected time of appearance of the end of T to the expected time of appearance of the apex of U in these cases, we found that the apex of U would have appeared before the end of T in 5 of the 17 cases. The interval Q-Uc in the four cases where the end of U could be measured accurately ranged from 98 per cent to 107 per cent with an average of 103 per cent, and from 80 to 110 per cent with an average of 102 per cent in all cases. This indicates that not only

apparently occurs at the normal time, the interval between the end of T and the apex of U is shorter than normal, that is 0.02 to 0.11 second with an average of 0.073 second.

In the cases of hypopotassemia with hypocalcemia (tables 2, 3, and 4) the U wave was more or less elevated in all cases. The Q-aU interval had an average of 103 per cent while the Q-U interval averaged 100 per cent of normal. These normal average values are to be expected, as we have seen that hypopotassemia tends to shorten while hypocalcemia tends to prolong slightly the Q-aU and Q-U intervals.

Th interval between the end of T and the apex of U ranged from 0.02 to 0.10 second with an average of 0.06 second. Due to prolongation of Q-Tc in these cases, this interval is less than in pure hypopotassemia.

The effect of administration of calcium on the Q-aU and Q-U intervals could be followed only in the four cases where the U wave was measurable before as well as after calcium. The changes of Q-aUc ranged from a decrease of 7 per cent to an increase of 4 per cent, with an average decrease of
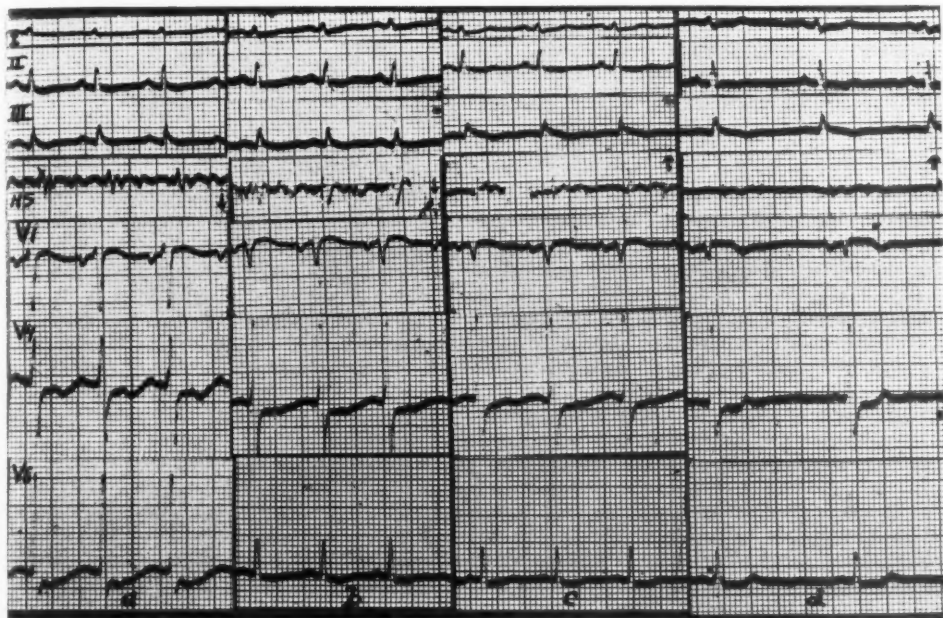

FIG. 9. Observation 4, table 3B. Reticulum cell sarcoma, terminal stage. Cachexia and vomiting. Heart sounds (HS) are synchronous with precordial leads in a and b, with limb leads in c and d. (a) Before beginning of medication. Serum potassium = 3.2, sodium = 145, calcium = 6.7, chlorides = 112, carbon dioxide = 16.4 mEq. per liter; total serum proteins = 4.9 Gm. per 100 cc. Extremely short S-T segments. T diphasic in all leads except V_1. U waves merged with T waves in the precordial leads. (b and c) After infusion, respectively, of 15 and 40 mEq. of potassium phosphate in saline. Progressive increase in voltage of the positive component of T and decrease in that of U. (d) After 45 mEq. potassium. Further elevation of T waves.

After administration of potassium the U wave became lower in all cases, and in two cases it became completely invisible. In the 13 cases where U could be measured before and after potassium, the changes of the Q-aTc interval ranged from a decrease of 10 per cent to an increase of 19 per cent, with an average increase of 0.15 per cent. The change of the Q-Uc interval in the 10 cases in which it could be measured both before and after potassium ranged from a decrease of 9 per cent to an increase of 14 per cent, with an average decrease of 0.5 per cent. The conclusion can thus be made that administration of potassium has no influence on the Q-aU and Q-U intervals. The changes of the distance from the end of T to the apex of U ranged from a decrease of 0.08 second to an increase of 0.02 second, with an average decrease of 0.016 second.

0.5 per cent. The changes of Q-Uc ranged from a decrease of 5 per cent to an increase of 5 per cent, with an average increase of 0.25 per cent. The distance from the end of T to the apex of U showed an increase of 0.01 to 0.09 second with the average being 0.052 second.

THE SECOND HEART SOUND AND ITS RELATION TO THE T AND U WAVES

A phonocardiogram was available only in 11 of the 25 cases of hypocalcemia described in table 2 and summarized in table 4. From these tables, it is apparent that in hypocalcemia the second heart sound begins much earlier than normal with respect to the T wave but

only slightly earlier with respect to the U wave. This sound begins from 0.01 to 0.10 second (on the average 0.061 second) later than the expected end of T for the heart rate and sex; this is 0.054 second later than in normal subjects. We must conclude, therefore, that in hypocalcemia the mechanical systole is prolonged, but not as much prolonged as the Q-T interval.

In the eight patients with pure hypopotassemia in which the heart sounds were registered (table 4), the second heart sound began on the average 0.015 second later than in normal persons in relation to the apex of T,

FIG. 10. Observation 2, table 3B. Lead II of figure 3 A, B and C, enlarged and superimposed to show the relation of the second heart sound to the T and U waves. See text, below.

0.017 second earlier in relation to the end of T, but only 0.008 second earlier in relation to the expected Q-T duration. In relation to the apex of U, it began 0.01 second later than in normal subjects. In hypopotassemia with hypocalcemia, the relation of this sound to the T wave is like that found in pure hypocalcemia. In our case of hypopotassemia with hypercalcemia the distance from the apex and end of T to the beginning of the second sound had the highest values encountered in any of our cases.

In the five cases of hypopotassemia with phonocardiograms, where potassium was given, the relations of the second heart sound to the electrocardiogram at the lowest potassium level were compared with those at the highest potassium level and the most normal configuration of the electrocardiogram.

It was found that the beginning of the second sound at the higher potassium level appeared on the average 0.004 second later with respect to the apex of T, 0.002 second later with respect to the end of T, and 0.005 second later with respect to the apex of U. These are insignificant changes. However, in three of our observations (table 3B, observations 2, 3, and 4), infusion of potassium caused relative normalization of the electrocardiogram, but the patients died a short time after the last tracing was taken. If we substitute for these preterminal trac-

FIG. 11. Observation 8, table 3B. Uremia due to obstruction of ureters in uterus carcinoma invading the bladder. The heart sounds (HS) are superimposed on lead V$_3$. (A) Serum potassium = 5.8, sodium = 143, calcium = 4.4, chloride = 79, carbon dioxide = 29.2, mEq. per liter. Pattern of hyperpotassemia with peaked, "tent-shaped" T waves. (B) Four weeks later, two days before death. Serum potassium = 3.0, sodium = 130, calcium = 3.15 mEq. per liter. Pattern of hypopotassemia with hypocalcemia. Depressed, prolonged S-T segments. Merging of T and U, with apex of the T plus U wave probably formed by U.

ings the tracing preceding them, taken at lower potassium levels but under better conditions of the circulatory system, we find that the second sound occurred on the average 0.028 second later with respect to the apex of T, 0.014 second later with respect to the end of T, and 0.01 second later with respect to the apex of U. These new values apparently show that correction of hypopotassemia causes the second sound to occur significantly later with respect to the T wave but only slightly later with respect to the U wave. This behavior is illustrated in figure 10, in which, during the course of potassium administration, the second heart sound occurs pro-

gressively later without any significant change in the heart rate. The question whether the changes of the second heart sound are caused by the administration of potassium alone, or also by the infusion of fluids in previously dehydrated patients, cannot be answered satisfactorily at the present time. Another possible source of error in the determination of the time relations of the second heart sound is that the rapid vibrations comprising the beginning of this sound were usually difficult to identify during the height of hypopotassemia but very easily seen after administration of potassium. Accordingly we may not have compared quite the same phenomena before and after potassium administration.

The effect of calcium administration on the second heart sound could be observed in a satisfactory manner only in one case (table 3B, observation 6 and fig. 7). In this case the second sound appeared 0.05 second later with respect to the apex of T, 0.01 second later with respect to the end of T, and 0.02 second later with respect to the apex of U. In another case (observation 7) there seemed to be no change in the relationships, but the T and U waves could not be differentiated exactly. In observation 8 of table 3B the second sound appeared 0.10 second earlier with respect to the apex of T, 0.09 second earlier with respect to the end of T, and 0.03 second earlier with respect to the apex of U when hypocalcemia developed, but in this case the serum potassium concentration also showed a drop from 5.8 to 3.0 mEq per liter, so that it is impossible to say which of these two factors had the greater role in provoking these changes.

Other Electrocardiographic Observations

The predominant cardiac mechanism in hypopotassemia was sinus rhythm; the heart rate in the cases shown in table 2 ranged from 46 to 120, averaging 82. Administration of potassium caused, on the whole, a slight increase in the heart rate, corresponding to an average decrease of 0.05 second in the R-R interval. Of greater importance is the presence of various cardiac arrhythmias in all of our own patients who showed a serum potassium level of less than 2.6 mEq per liter. One case (observation 2) showed an upper nodal rhythm, one case (observation 5) atrial premature beats, one case (observation 7) ventricular premature beats partly appearing as bigeminal rhythm and one case (observation 3) both atrial and ventricular premature beats, at times alternating with sinus beats. In all cases the arrhythmia disappeared upon administration of potassium.

The P waves were taller at the height of hypopotassemia in eight of our personal cases. The P-R interval was slightly longer at the height of hypopotassemia in three of the eight cases, but did not exceed 0.19 second at any time. The duration of the QRS interval showed no measurable changes except in observation 5 of table 3B, which was discussed on page 805.

Discussion

One of the most important results of this study is that the duration of the Q-T interval, corrected for the heart rate and sex, is not prolonged in cases of pure hypopotassemia and is not influenced by administration of potassium. This conclusion is corroborated by our finding that the components of this interval (the QRS complex, the S-T segment and the T wave) all have a normal duration in pure hypopotassemia.

As mentioned in the introduction, in most of the reports describing a prolonged Q-T duration in hypopotassemia the U wave was not adequately differentiated from the T wave and the Q-U duration was measured instead of the Q-T duration. The Q-U duration in normal persons is 40 per cent to 70 per cent greater than the Q-T duration. As we found the Q-U duration to be normal in hypopotassemia, we would expect that measurement of Q-U instead of Q-T would give only very high values for the corrected Q-T duration. The apparent Q-T duration determined in this way would depend on the heart rate; it would increase from about 140 per cent at a heart rate of 100 to about 170 per cent at a heart rate of 45.[22] The values of the apparent Q-T calculated by measuring Q-U instead of Q-T in the cases of table 3A actually lie within this range. A gradual increase in the apparent Q-T duration with increasing hypopotassemia reported in some cases[3, 4, 30, 33] could have been simulated either by a decrease in the heart rate or by an increase in the voltage of the U waves. Such an increase would cause the duration of these waves to appear longer, as the normally almost isoelectric terminal section of U would then be more easily separated from the level U-P interval. To be sure, this explanation applies only as long as the apparent Q-T interval is between 140 per cent and 170 per cent.

The lesser degrees of Q-T prolongation (values of 110 per cent to 140 per cent) reported in hypopotassemia[33] cannot be explained by measurement of Q-U instead of Q-T, and must, therefore, correspond to a true prolongation of Q-T. In these cases factors other than hypopotassemia must be held responsible for this prolongation. One of these factors is hypocalcemia, as we have seen in the present study. Many of the conditions in which hypo-

potassemia occurs (for instance, diarrhea, vomiting and renal insufficiency) are often also accompanied by hypocalcemia.* However, a prolongation of Q-T, which ranged from 105 per cent to 140 per cent and, therefore, could not have been caused by inclusion of a U wave, was found in a considerable number of hypopotassemia cases which had a serum calcium above 4.0 mEq per liter.[33] It is possible that in some of these cases the total serum calcium was normal but the ionized calcium was low. Almost one-third of the group had acidosis and another one-third had renal insufficiency, and Q-T may be prolonged in these conditions independently of the serum calcium level.[27, 22a, 20 (par. 536, 736)] In the present study we have attempted to include only cases of hypopotassemia accompanied by as few as possible additional metabolic alterations in our table 1. Cases of familial periodic paralysis and those of potassium depletion with fixation of potassium due to infusion of potassium-free dextrose solutions seemed to answer these requirements best.

Our measurements failed to show any changes in the duration of the T wave in hypopotassemia. It can be readily understood that the inclusion of the U wave in the Q-T interval will cause the impression of a broadening and rounding of the shape of the T wave which has been described as accompanying the prolongation of Q-T.[8, 9, 10, 28, 32] According to our own measurements and those of other investigators, the duration of the S-T segment is unchanged in hypopotassemia.

The instances in which the S-T segment appeared to increase in length proportionately to the Q-T interval[33] can probably be explained by difficulties in determination of the onset of the T wave in the cases with descending and sagging S-T segments, since, as mentioned in the section on the S-T segment, this segment terminates in such cases in the nadir of the negative or negative-positive T wave without any visible change in slope. If the duration to the nadir of such a T wave is measured as S-T, high values will be obtained. The possibility of some other factors causing S-T prolongation in some of the reported cases can, however, not be entirely ruled out.

According to our measurements, the duration of QRS showed no appreciable change during de-

velopment or regression of hypopotassemia in almost all of the cases which were studied. One of our cases (observation 7 of table 3B, and fig. 5) had exhibited a right bundle branch block pattern, but as this pattern remained unchanged after administration of potassium it is probable that it was present even before the appearance of hypopotassemia. Another case (observation 5 of table 3B, and fig. 6) developed a peculiar slurring at the foot of the descending limb of R which we considered as belonging to the QRS group and which increased the duration of QRS to about 0.12 second. This case was discussed on page 805, where two similar cases from the literature were also mentioned. Recently two cases showing a similar pattern during diabetic acidosis associated with hypopotassemia were reported.[14a] In these cases the slurring became less pronounced or disappeared completely with disappearance of acidosis although the serum potassium level continued to decrease; this indicated that the changes of QRS were more related to acidosis than to hypopotassemia. A slurring of the ascending branch of the S waves in all standard limb leads appeared at the height of hypopotassemia in one case of familial periodic paralysis and was interpreted as right bundle branch block with a QRS duration of 0.20 second.[34] In this case the apparent slurring could have corresponded to a very steep ascending S-T segment, but this cannot be decided definitely as the precordial leads were not registered. A pattern which was interpreted as an intraventricular conduction disturbance appeared in calves raised on a potassium-free diet.[20] In the cases which showed the above-mentioned changes of QRS and in which chest leads were taken, the slurring was confined entirely to the terminal portion of QRS while the intrinsicoid deflection appeared at an approximately normal time. It is possible, therefore, that the pattern may not represent an intraventricular conduction disturbance but rather a terminal slowing in the depolarization process in each heart muscle element. At any rate, the QRS changes described above are rare in hypopotassemia and seem to appear only at very low serum potassium values or in combination with other factors such as acidosis.

Measurements of the duration of the U wave could not be undertaken since in the vast majority of the cases of hypopotassemia the U wave begins before the end of the T wave and the onset of U thus cannot be determined accurately. The apex of the U wave and the end of the U wave were found to appear slightly earlier than in normals, but the difference is very small.

Our studies have, therefore, led us to the conclusion that pure hypopotassemia causes no appreciable changes in the duration of any of the components of the ventricular electrocardiogram. The most characteristic changes

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* In many cases it was concluded that hypocalcemia could not have played any role in the prolongation of Q-T because Q-T showed no shortening after injection of calcium (fig. 4, 6a). If Q-U was measured instead of Q-T in these cases, we would not expect any shortening even in the presence of hypocalcemia, as we have seen that Q-U is not affected appreciably by calcium.

are those of the voltage and configuration of these components; they consist of a "sagging" of the S-T segment,[2, 6, 7a, 10, 14a-b, 27a, 28, 31, 32, 34] depression of the T wave[2, 6, 7a, 10, 14a-b, 27a, 28, 31-33, 34n] and elevation of the U wave.[3, 4, 9, 14a, 27a, 33] These changes in persons showing a normal initial electrocardiogram and in typical unipolar leads from the anterior epicardial surface of the left ventricle are represented schematically in figure 12 which was constructed to scale for a heart rate of 60.

With progressive development of the hypopotassemia pattern the normally ascending S-T segment becomes at first horizontal (patterns I–II), then progressively more descending (patterns III–V). As long as the T wave still remains upright the S-T segment may develop an upward concavity and assume the "sagging" configuration considered typical of hypopotassemia (pattern IV). If the T wave becomes inverted, the concavity of S-T becomes directed downward (pattern V). The T wave becomes progressively lower as hypopotassemia develops. In pattern I it is lower than normal, but still exceeds the voltage of the U wave in the same lead. In pattern II the T wave becomes lower than the U wave. In pattern III, T becomes diphasic and of low voltage, with an initial negative phase which is lower than the final positive phase. In pattern IV the negative phase is higher than the positive phase. Finally T becomes completely negative (pattern V). At some time the voltage of a diphasic T wave may become so small that it becomes practically isoelectric and the ventricular complex seems to consist entirely of an S-T segment and a U wave (pattern III). The U wave shows a progressive increase in voltage with increasing hypopotassemia. We have never seen any changes in the direction of the U wave in pure hypopotassemia.

The fact that U waves were found only in 42 per cent to 55 per cent of the cases in a large series of persons with low serum potassium[4, 33] can be explained if we assume that in these studies only U waves which were clearly separated from the T waves were recognized as such.

The maximal changes of each of the three components of the ventricular complex (S-T,

T and U) influenced by hypopotassemia appear in different leads. The elevation of the U wave is most pronounced in the leads which show the highest upright U waves in normal subjects, that is, in leads V_2 or V_3. Lead aV_R, which shows negative U waves normally, usually shows accentuation of these negative U waves. Accordingly, CR leads were found to show higher U waves than V leads.[6b] Lead aV_L as a rule shows the lowest voltage of U in hypopotassemia and is, therefore, useful in
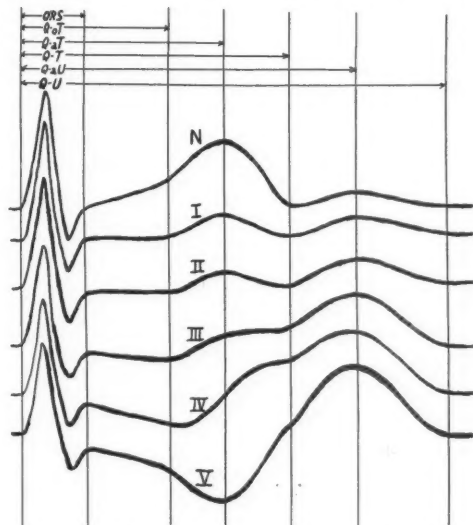
FIG. 12. Schematic diagram showing five phases (I–V) in the development of the typical hypopotassemia pattern in leads facing the anterior left ventricular epicardial surface. N = normal pattern. The diagram was drawn to scale for a heart rate of 60. The vertical lines designate points of the electrocardiogram used for the measurement of the intervals. See text.

recognizing the true duration of the T wave and of the Q-T interval. The changes of the T wave and the S-T interval, on the other hand, are greatest in leads showing the greatest positive area of QRS. These are the left ventricular epicardial leads and in vertical hearts leads II and III, in horizontal hearts leads I and II.

The most typical pattern of hypopotassemia is characterized by an S-T segment and T wave of opposite polarity to a U wave of increased voltage. The total appearance was compared

with a letter "S" lying on its side.[27a] This pattern appears most frequently in leads which show normally the combination of a relatively low T wave and a relatively high U wave, that is, in the precordial leads V_3, V_4 and V_5. In the precordial leads situated further to the left, the U wave is usually very small and, even if markedly elevated in comparison with its normal size, may still remain absolutely small and therefore inconspicuous. In the precordial leads situated further to the right, the T wave usually remains positive and in many cases merges with an elevated positive U wave. These leads show frequently a huge positive T-plus-U wave, the apex of which probably corresponds neither to the apex of T nor to the apex of U, but to a point situated somewhere between them. In the limb leads, which reflect electrical events of a larger area of heart muscle than the precordial leads, the possibility of both the U-wave and the T-wave patterns of hypopotassemia being registered in the same lead is greater than in the precordial leads. In vertical hearts the characteristic pattern appears predominantly in leads II, III and aV_F, while in horizontal hearts it appears usually in leads I, II and, with reversed polarity, in lead aV_R.

The magnitude of the changes of each of the three main components may be independent of that of the other two; it is in general proportional to the degree of hypopotassemia, but may vary greatly from person to person. In some cases the U-wave changes predominate while the S-T and T-wave changes do not exceed those of pattern I. This is theoretically most likely to occur in persons who normally show high T and U waves. In other cases the S-T and T changes are very pronounced while the U waves are only slightly increased in voltage. This is likely to occur in persons showing low T and U waves and a tendency to a horizontal course of S-T prior to the appearance of hypopotassemia. The processes which modify the hypopotassemia pattern may have been present before the onset of hypopotassemia or they may appear simultaneously with the development of hypopotassemia or following it. In any case the electrocardiogram will be affected by the combination of changes due to the hypopotassemia and to other factors.

Any attempt to classify the electrocardiographic pattern of hypopotassemia according to the severity of the condition must take into consideration the factors mentioned above. The patterns represented in the figure 12 of this paper were constructed deliberately in such a way that the changes of the S-T segment, of the T wave and of the U wave develop simultaneously and in a constant relation to each other. Many other patterns could be constructed if combinations of S-T and T of one pattern with U of another pattern were used. The number of different patterns of hypopotassemia found in the precordial leads facing the epicardial surface of the left ventricle is accordingly much greater than indicated in figure 12. For future studies it may become useful to describe these patterns as consisting of S-T, T and U changes of different degree, corresponding to the changes represented in the four patterns of figure 12.

One method of expressing the severity of the hypopotassemia pattern numerically might consist of measuring the distance between the apex of T and the apex of U. In the normal pattern this distance would be negative; in pattern I it would have small negative values, in pattern II these values would be positive. In patterns III and IV the distance would be measured from the apex of U to the negative apex (nadir) of a diphasic T wave. The values would be increasingly positive in patterns II through V. The highest positive difference in any one of the limb or precordial leads would be used. The disadvantage of this method is that it would measure the absolute differences in millimeters or millivolts, and these would be influenced by extracardiac factors such as the distance of the heart from the chest wall and presence of edema, pericardial or pleural effusion and similar influences. One way to avoid this influence could be to express the difference not in absolute values but as a percentage of the highest QRS amplitude. It should be emphasized that this method can be used only if the electrocardiogram definitely shows one of the hypopotassemia patterns described above; applied to other electrocardiographic patterns, it will give misleading results. We have not yet applied this method on a large scale, but we expect to do so in future studies.

Since the same pattern found in two different individuals may represent a considerably different degree of the deviation from the initial pattern of these individuals, no conclusion regarding the se-

verity of hypopotassemia can be made without the knowledge of the electrocardiographic pattern preceding the development of the changes due to the hypopotassemia.

Some authors[27a] have attempted to correlate the electrocardiographic pattern of hypopotassemia with the level of serum potassium. They described a lowering of the T wave at the level of 3.5 to 4.0 mEq. per liter and a "double hump" pattern at the serum potassium level between the 2.5 and 3.5 mEq. per liter. The two humps (representing the T wave and the U wave) change their mutual relations in such a way that at the higher serum potassium levels T is higher than U and at the lower serum potassium levels U is higher than T. Finally, a pattern similar to the recumbent letter S was said to correspond to the serum potassium level of about 2 mEq. per liter. This method does not take into account the factors discussed in the preceding paragraphs; furthermore, the absolute serum potassium level is only indirectly responsible for the hypopotassemia pattern (see page 825).

An attempt to correlate the electrocardiographic changes with the level of serum potassium and the cumulative potassium balance was undertaken recently[23a]; no correlation was found. The electrocardiograms were classified according to the ratio of the voltages of the T and the U waves. Apparently leads with the highest U wave were used for this purpose. One of the disadvantages of this method is that considerable variation of the T/U ratio may occur in the transitional zone due to the change of the heart position during different phases of respiration. T may normally vary from positive to notched, positive-negative or negative under these conditions and U may also change its voltage to some extent depending on the heart position in these leads. This method is further limited by the fact that it can be used only for milder degrees of hypopotassemia, in which the T wave remains positive.

Bellet and co-workers[3] subdivided the changes of the ventricular complex observed by them in 79 cases with hypopotassemia into five patterns. Pattern 1 was characterized by depression of S-T, accompanied by positive T waves with lengthening of the Q-T interval. In our opinion, this pattern in most cases corresponds to the patterns III through V of our figure 12; we assume that in these cases the U wave was incorporated into the T wave. In those cases of pattern 1 in which a distinct U wave was reported, this pattern may have corresponded to our pattern I in which true Q-T prolongation was present due to other causes than hypopotassemia. Pattern 2 of Bellet and co-workers was characterized by inversion of the T wave accompanied by Q-T prolongation, frequently followed by a U wave. In patterns 2a and 2c, S-T was slightly elevated or isoelectric and followed by a terminal downward dip of the T wave, as is seen in the late phase of myocardial infarction. We consider that these patterns are not produced directly by hypopotassemia but are caused by concomitant myocardial ischemia, pericarditis or other conditions. In pattern 2b the inversion of T was accompanied by depression of S-T. We assume that in this pattern the U waves were considered as T waves, so that this pattern actually corresponds to our pattern V.

Patterns 3a and 3c of Bellet and associates were characterized by positive T waves of normal amplitude, beginning immediately after QRS without an isoelectric S-T segment, and accompanied by a prolonged Q-T duration. We consider that in these patterns the T wave was completely merged with the U wave in the leads in which this pattern appeared; it would accordingly correspond to a variation of our pattern III in which the depression of S-T is of less than usual and the elevation of U of more than usual magnitude (fig. 4A, in leads V_1 and V_2 of fig. 3A and in leads II and V_2 of figure 6d). In pattern 3b a definite isoelectric S-T period was present; this pattern was rare and observed usually in the presence of "alkalinosis with or without hypocalcemia." This pattern corresponds to the modification of the hypopotassemia pattern seen in the presence of a low ionized serum calcium and discussed later on page 825.

Pattern 4 of Bellet and his colleagues was characterized by an upright but almost isoelectric T wave, followed by a U wave. This pattern evidently corresponds to our patterns I or II. It may appear even in normal persons in the transition zone of T, and would be diagnostic of hypopotassemia only when it appears in left precordial leads as well or when a previous normal tracing is available for comparison. Finally, pattern 5 of Bellet and co-workers showed a T wave of normal amplitude and normal Q-T duration, followed by an "unduly prominent U wave." This pattern would correspond to our pattern II appearing in a person with initially high T waves and steep S-T segments.

In the recognition of the electrocardiographic pattern of hypopotassemia, there are two main problems of differential diagnosis: First, other factors than hypopotassemia may cause some or all of the features of the hypopotassemia pattern to appear in a given electrocardiogram. Second, a true hypopotassemia pattern may be atypical or obscured by electrocardiographic changes caused by other factors.

Pointed, inverted T waves or diphasic (positive-negative) T waves do not resemble the hypopotassemia pattern sufficiently to cause any confusion even in the presence of a depressed S-T segment. However, many clinical conditions unrelated to hypopotassemia may

present a depression of the S-T segment with a horizontal or downward course, accompanied by diphasic (negative-positive) or inverted T waves, such as are encountered in the hypopotassemia pattern shown in figure 12. If the U waves which accompany these patterns are very low or absent, hypopotassemia can be practically excluded. The higher the U wave, the greater the probability that a true hypopotassemia pattern is present.

The suspicion of a hypopotassemia pattern does not usually arise if the S-T and T changes are opposed to the main QRS deflection in all leads (as in ventricular hypertrophy and strain patterns, and intraventricular conduction disturbances). The S-T and T changes caused by diffuse coronary insufficiency are independent of the QRS direction and may sometimes resemble the S-T and T changes of hypopotassemia; the same is true of the digitalis pattern. In the latter the Q-T duration is usually shortened while the apex and apparently the beginning of the U wave appear at a normal time; therefore the end of the T wave is easily recognizable and is frequently separated from the onset of the U wave by an isoelectric segment. Accordingly, if the negative phase of the T wave is followed by a short positive phase separated from the U wave by an isoelectric interval, the digitalis pattern and not the hypopotassemia pattern is likely to be present. The unchanged Q-T duration in hypopotassemia associated with a slightly earlier appearance of the U wave cause, in almost all cases of hypopotassemia, a merging of the terminal part of the T wave with the U wave even if the latter is not appreciably elevated.

U waves are present in all normal subjects and in nearly all patients[20, 22]; they may reach 0.15 millivolt in the standard limb leads and 0.2 millivolt in precordial leads.[20] Unusually high U waves may appear in the absence of hypopotassemia after exercise, in bradycardia, in athletes, in hypertension, and in dying hearts.[20, 22] Accordingly, it is impossible to make the diagnosis of hypopotassemia only on the basis of elevated U waves not accompanied by characteristic changes of T and S-T until the more exact criteria discussed on page 820 are available.

The greatest diagnostic difficulties are encountered in patients in whom the fully developed hypopotassemia patterns, including both the T and S-T changes and the U-wave changes, are seen, but in whom no reason for loss of potassium is found and in whom the serum potassium is not low. Striking examples of this may be found in patients who are being treated at the same time with digitalis and quinidine. In these patients depression of S-T and diphasic T waves characteristic of the digitalis pattern are combined with elevated U waves which apparently also appear earlier and often show partial merging with the T waves, as in the typical hypopotassemia pattern. The similarity may become so great that the two patterns may become practically indistinguishable. In view of this similarity we have even considered the possibility that this digitalis-quinidine pattern may be due to a redistribution of intracellular and extracellular potassium similar to that found in hypopotassemia. This subject will be discussed in a separate communication.

A pattern bearing a superficial resemblance to the more advanced hypopotassemia patterns may appear in advanced hyperpotassemia. In such instances a wide S wave of a greatly prolonged QRS complex may be mistaken for a horizontal S-T segment while the greatly prolonged, rounded P wave may be mistaken for a U wave. Multiple chest leads will almost always enable the correct diagnosis, since in some of these leads the voltage and slope of the terminal part of QRS and of the P waves will be of a sufficient magnitude to make their identification certain.

The appearance of peaked P waves,[27, 14a] A-V conduction disturbances[6, 31, 33, 34, 34a] and ectopic rhythms,[2, 7a, 12a, 14a, 31] while in itself not diagnostic of hypopotassemia, may serve as corroborating evidence of the existence of this condition if the other electrocardiographic criteria are equivocal.

The recognition of the true hypopotassemia pattern may be difficult in all cases in which the T and U waves are merged. In the majority of the cases in which a sufficient number of standard and unipolar leads has been registered, a definite notch or kink between the descending or ascending limb of T and the ascending limb of U is present at least in some of these leads.[21] The best leads for the detection of this kink

are leads V_3, V_4 and aV_L. However, in some cases the merging of T and U may be complete and no kink is visible in any of the leads registered. It may be difficult to determine whether the pattern which thus results represents the hypopotassemia pattern with a Q-T interval of normal duration accompanied by merging of T and U or whether the pattern is produced by a true prolongation of the Q-T interval with an absent or invisible U wave. This variant of the hypopotassemia pattern may cause a casual observer to decide against hypopotassemia because what appears as the T wave is increased in height. Such cases require special procedures in order to decide whether the questionable wave is a T wave or a T + U wave.

The first of these procedures is the measurement of the duration of the questionable wave and of the intervals from the beginning of QRS to the onset, apex and end of this wave. After correction for the heart rate and sex,[22] these intervals are compared with the same values in normal persons. Such a comparison will show whether these intervals approach most closely the normal values for the T wave or those for the U wave. Normal values can be used for comparison since in pure hypopotassemia these intervals show only insignificant deviations from the normal.

The second and more complicated procedure is the registration of a phonocardiogram synchronously with the electrocardiogram. Where multiple channel electrocardiographs are not available for routine use it has been found helpful to register the precordial lead V_3 through a magnetic microphone in contact with the chest wall, to visualize the time relation between the second heart sound and the T and U waves. In none of the more than 1000 cases with normal duration of QRS studied by us in this way did the second heart sound begin later than 0.03 second before the apex of the U wave. Accordingly, the appearance of the second sound later than 0.03 second before the apex of a questionable wave proves definitely that this wave is a T wave and not a U wave. On the other hand, the appearance of the second sound earlier than 0.03 second before the apex of a questionable

wave makes it almost certain that this wave is a U wave.

In none of the 1000 personal cases referred to above did the second sound begin earlier than 0.03 second before the apex of the T wave, and among all the published cases with heart sounds available to us this occurred only in one case (observation 8, table 2). This was a case of uremia with a serum calcium level of 2.4 mEq. per liter, a Q-Tc of 146 per cent, and a second sound beginning 0.11 second before the apparent apex of T. The occurrence of the second sound 0.03 second before the apex of the T wave was observed in two of all the published cases (observations 7 and 9 table 2); these were cases of uremia with serum calcium respectively of 3.0 and 3.15 mEq per liter and corrected Q-T (Q-Tc) of 142 and 145 per cent. In one of our own cases (observation 8 of table 3B, a patient with uremia who showed a serum calcium level of 3.15, a serum potassium level of 3.0 mEq. per liter and a Q-Tc of 130 per cent), the second sound began 0.02 second before the apex of the T wave. In none of the other observed or published cases did the second sound begin before the apex of the T wave. All four cases mentioned above were cases of uremia; in one case the serum potassium level was low, in the other three[1] it was not measured. The U wave could not be seen in these cases, but in all of the cases the apex of the U wave would have coincided with the T wave if the Q-U interval were of normal duration. It is very likely, therefore, that, in cases of hypocalcemia with marked Q-T prolongation associated with elevation of the U wave, summation of the T and U waves causes the formation of a new apex situated between the true apices of T and U, and that this apex is measured instead of the apex of T in these cases. In none of the published cases of hypocalcemia due to hypoparathyroidism did the second sound occur before the apex of the T wave. It can thus be concluded that the appearance of the second sound before the apex of the questionable wave makes it most likely that this wave is a U wave. The exceptions to this rule are very rare and seem to be confined to cases of hypopotassemia with hypocalcemia.

The third procedure for the differentiation of T and U consists of the administration of substances modifying the electrocardiogram in such a way that the pattern becomes more typical. It has been shown that in the case of an electrocardiographic pattern due to deficiency of two electrolytes, the administration of one of these will more clearly demonstrate the deficiency of the other.[4] The almost selective action of calcium on the S-T segment makes it possible to shorten this segment by

means of an intravenous injection of 10 to 20 cc. of a 10 per cent calcium gluconate solution. The shortening of the S-T segment causes an earlier appearance of the apex and end of the T wave and a better separation of the T wave from the U wave (figs. 7, 8A). This method can be successfully applied not only in the cases of hypopotassemia showing long S-T segments, in which hypocalcemia may be suspected, but also in cases with normal duration of the S-T segment in which the T and U waves are merged (fig. 8B). The shortening of the S-T segment following calcium administration in cases with normal or high serum calcium is less pronounced than in cases with hypocalcemia, but in most of the cases it does result in separation of the T wave from the U wave. As has been pointed out previously, the action of calcium is very transient and may last for 1 or 2 minutes only[4]; therefore the electrocardiogram has to be recorded during and immediately after the calcium injection.

The administration of potassium may also cause separation of a questionable T + U wave into its components by elevating the T wave and lowering the U wave. However, in order to be safe, this procedure can be adopted only after a thorough evaluation of the clinical data, and must be carried out very slowly and under constant electrocardiographic observation with a direct-writing instrument. This procedure is, therefore, much more laborious and time-consuming than the intravenous injection of calcium, and is seldom required for purely diagnostic purposes.

The diagnosis of the hypopotassemia pattern may be difficult in the presence of other electrocardiographic abnormalities not due to hypopotassemia. In the case of marked intraventricular conduction disturbances (bundle branch block, ventricular premature beats) the recognition of the hypopotassemia pattern is difficult since the T and U waves merge, the degree of merging being proportional to the increase in the duration of QRS. On the other hand, in the case of right bundle branch block or extrasystoles originating in the left ventricle the second heart sound occurs earlier in relation to the T wave and may even occur before the apex of T. We have found that the purest hypopotassemia pattern

appears in leads in which the total area of QRS is nearest zero. For instance, in figure 5 leads V_5 and V_6 show a marked depression of S-T and a distinct kink between the low T wave and an elevated U wave, while lead V_2 does not differ in its configuration from that of typical right bundle branch block.

Marked S-T and T changes due to the currents of injury in myocardial infarction or to other factors may be expected to obscure the electrocardiographic hypopotassemia pattern. The appearance of deep inverted U waves in left precordial leads in the presence of hypopotassemia reported in two cases[16a, 29a] was probably due to the fact that the individuals who developed the hypopotassemia pattern had negative U waves in these leads previously. The recognition of the hypopotassemia pattern may be difficult in the presence of tachycardia and/or prolonged P-R interval because of the merging of the P wave with the U wave; this has been discussed earlier.[21]

The detailed studies of the electrocardiographic pattern of hypocalcemia included in the present investigation were carried out in order to be able to evaluate the influence of hypocalcemia on the electrocardiographic pattern of hypopotassemia. Our method of measurement of the components of the Q-U interval, applied to the electrocardiograms of hypocalcemia compiled from the literature, confirmed the frequently described prolongation of the S-T segment with normal duration of the T wave[3, 4, 9, 11, 20, 33, 37] which results in a prolonged duration of the Q-oT, Q-aT and Q-T intervals, corrected for the heart rate and sex. Actual measurements of the S-T segment in the electrocardiogram of hypocalcemia have been reported previously,[11, 37] but the method of measurement was not defined exactly.[22] All cases studied by us with a serum calcium lower than 4.0 mEq. per liter had a Q-aT duration exceeding the normal upper limit of 63 per cent of the expected Q-T duration, corrected for the heart rate and sex. The time of appearance of the U wave and its duration, as evident from the nearly normal duration of the Q-aUc and Q-Uc intervals, is not changed in hypocalcemia. Accordingly, the U wave is visible as a separate wave only in cases with not very marked Q-T prolongation, for example, in not very severe hypocalcemia; in the

cases with pronounced Q-T prolongation the U wave is merged with T or even completely absorbed by the latter.

The electrocardiographic pattern of hypopotassemia accompanied by hypocalcemia consists of a combination of the patterns of pure hypopotassemia and pure hypocalcemia. As a result, the hypopotassemia patterns of figure 12 become modified by a lengthening of the S-T segment. A Q-oT duration exceeding 74 per cent of the Q-T duration expected for the heart rate and sex makes it almost certain that hypocalcemia is present. Due to the prolongation of the Q-T duration without a corresponding increase of the Q-U duration the degree of merging between T and U is greater than in pure hypopotassemia. In none of the cases seen by us was this prolongation of Q-T great enough to cause a complete swallowing up of the U wave by the T wave, but such a possibility must be taken into consideration. This could have been one of the factors responsible for the apparently normal configuration of the electrocardiogram in case 6 of Currens and Crawford,[7] in which an extremely low serum potassium was present with a low serum calcium.

The administration of potassium in cases with a hypopotassemia pattern modified by hypocalcemia causes the configuration of the S-T segment, the T waves and the U wave to change toward normal, but the duration of S-T remains unchanged (fig. 8B). The administration of calcium shortens the S-T duration, while the electrocardiographic features of the hypopotassemia pattern remain unchanged (fig. 8A). Hypocalcemia may cause a lowering or inversion of the T wave.[4, 25, 33] and the hypopotassemia pattern may accordingly appear to be more severe as far as the T-wave changes are concerned if hypocalcemia is also present. Administration of calcium in such cases will disclose more truthfully the electrocardiographic changes due to hypopotassemia.

The term "hypopotassemia" has been used in this paper in order to designate the condition associated most commonly with the described electrocardiographic pattern. The correlation with the serum potassium level has been made because the electrocardiographic changes usually parallel this level. We are aware, however, of reports describing in some cases the lack of electrocardiographic abnormalities in spite of a definitely low serum potassium on one hand and the appearance of an electrocardiographic pattern of hypopotassemia with a normal or high serum potassium level on the other hand. In the recent review of this problem[27] it was estimated that only 80 per cent of patients with serum potassium level below 3.5 mEq. per liter show suggestive electrocardiographic abnormalities. It is very likely that a better correlation could be obtained if the electrocardiographic diagnosis were improved by the routine use of the methods described in the present paper.

Up to the present time no exact correlation of the electrocardiographic pattern of hypopotassemia with either the total body potassium or the extracellular or intracellular potassium concentration could be obtained. According to our opinion, the best correlation would be expected with the potassium gradient across the cell membrane and not with the intra- or extracellular potassium concentration alone. A study of this problem by correlating the electrocardiographic pattern with the ratio of the potassium concentrations in the plasma and in the blood cells has been conducted by us for some time, but the available data are not yet sufficient for a final evaluation. Since sodium replaces the potassium in the cells if the latter is lost, the simultaneous study of the relation between the intra- and extracellular sodium concentration appeared to us imperative. Other electrolytes, and possibly the pH of the blood, may be partly responsible for the development of the pattern, but there is no established evidence for this as yet.

The lack of understanding of the precise etiology of the hypopotassemia pattern does not prevent the practical application of the electrocardiographic method for the diagnosis of the clinical manifestations of hypopotassemia. The seriousness of this condition for the patient cannot be measured by the estimation of the total body potassium loss or of the level of serum potassium, but by the amount of impairment of the function of the muscle cell. The electrocardiogram portrays

the reversible changes in the function of the heart muscle with great rapidity and exactitude, and it appears very unlikely that the response of the skeletal or smooth muscle is different from that of the myocardium. A correlation study between the degree of muscular weakness or other studies of the function of the skeletal muscle in patients with hypopotassemia and the electrocardiogram is contemplated in order to prove this assumption.

SUMMARY

1. The electrocardiograms of 25 cases of hypocalcemia, 25 cases of hypopotassemia without hypocalcemia (6 of these our own patients) and 8 cases of hypopotassemia with hypocalcemia (2 of these our own patients), as well as 1 case of our own of hypopotassemia with hypercalcemia, were subjected to detailed examination. The components of the Q-U interval (the Q-oT, Q-aT, Q-T, Q-aU and Q-U intervals from the beginning of QRS to the origin, apex and end of T and the apex and end of U, respectively) were measured. These components were also measured in 16 cases of hypopotassemia without hypocalcemia before and after potassium administration, and in 5 cases of hypopotassemia with hypocalcemia before and after calcium administration.

2. The results of our measurements were compared with the values obtained in normal subjects for the corresponding heart rate and sex. These results are summarized in table 4. It was found that in pure hypopotassemia the duration of none of the components of Q-U deviates appreciably from the normal values. The widespread impression that Q-T is prolonged in hypopotassemia has resulted either from the inclusion of the U wave in the Q-T interval, or from the presence of other coexisting factors. Our results showed that in hypocalcemia the duration of the Q-T interval and its components is prolonged to a degree corresponding to the prolongation of the S-T segment, but the Q-aU and Q-U durations are unchanged. In hypopotassemia with hypocalcemia, Q-T and its components are prolonged as in hypocalcemia; the degree of merging between T and U increases with the increased Q-T duration. The administration of either potassium or calcium corrected only the electrocardiographic changes due to the deficiency of this particular electrolyte while the changes due to the deficiency of the other remained.

3. The phonocardiogram was taken synchronously with the electrocardiogram in all of our own patients who are included in this study. The mechanical systole in hypopotassemia is either of normal duration or shortened; in hypocalcemia it is prolonged, but not as much as the duration of the Q-T interval. The beginning of the second sound was never observed more than 0.03 second before the apex of the U wave. It was found only exceptionally (in some cases of hypocalcemia) before the apex of the T wave.

4. The typical electrocardiographic pattern of hypopotassemia consists of a progressing depression of the S-T segment, lowering and inversion of the T wave and increase in amplitude of the U wave in left precordial leads. Five typical patterns of hypopotassemia were constructed according to the degree of development of these changes. QRS changes were found only occasionally. Ectopic rhythms usually appeared in the more severe cases.

5. The differential diagnosis between the true hypopotassemia pattern and patterns similar to it, but due to other factors, was discussed. The pattern most similar to the hypopotassemia pattern is that appearing in some cases after administration of digitalis together with quinidine. The recognition of the atypical hypopotassemia patterns was also discussed. Among these the most difficult is the pattern with merging of the T and U waves without a distinct and visible kink in the merged wave. For the differentiation of this pattern from a true prolonged Q-T, three methods are recommended.

6. The degree of development of the electrocardiographic pattern of hypopotassemia is in general parallel to the decrease in the serum potassium level, but there are some exceptions. Studies are in progress to correlate the hypopotassemia pattern with the ratio of intracellular to the extracellular potassium concentration.

SUMARIO ESPAÑOL

Analisis detallado de electrocardiogramas en pacientes con hipopotasemia sin hipocalcemia reveló que el intervalo Q-U y sus componentes (Q-oT, Q-aT, Q-T, and Q-aU) tienen esencialmente la misma duración que en sujetos normales con el mismo pulso y sexo. El patrón típico de hipopotasemia se caracteriza por depresión progresiva de S-T, aplastamiento e inversión de T y aumento de U en las derivaciones precordiales del lado izquierdo. En hipopotasemia con hipocalcemia S-T y Q-T pero no Q-U, estan prolongados, causando un aumento en el grado de fundición entre T y U. Tres metodos de diferenciación entre T y U's completamente fundidas y ondas T verdaderas de Q-T prolongados se describen.

REFERENCES

[1] Barker, P. S., Johnston, F., and Wilson, F. N.: The duration of systole in hypocalcemia. Am. Heart J. **14:** 82, 1937.

[2] Bellet, S., Nadler, C. S., Gazes, P. C., and Lanning, M.: Effect of vomiting due to intestinal obstruction on the serum potassium. Am. J. Med. **6:** 712, 1949.

[3] —, Steiger, W. A., Nadler, C. S., and Gazes, P. C.: Electrocardiographic patterns in hypopotassemia. Am. J. M. Sc. **219:** 542, 1950.

[4] —, and Finkelstein, D.: Significance of Q-T prolongation in the electrocardiogram. Am. J. M. Sc. **222:** 263, 1951.

[5] —, Nadler, C. S., Gazes, P. C., and Lanning, M.: The effect of vomiting due to intestinal obstruction on the serum potassium. Gastroenterology **12:** 49, 1949.

[6] Brown, M. R., Currens, J. H., and Marchand, J. F.: Muscular paralysis and electrocardiographic abnormalities. J.A.M.A. **124:** 545, 1944.

[6a] Craige, H. R.: Paper presented at the meeting of the New England Cardiovasc. Soc., Dec., 1952.

[6b] Carlsten, A.: Choice of indifferent electrode in the study of the electrocardiographic afterpotentials, Acta med. scandinav. **145:** 72, 1953.

[7] Currens, J. H., and Crawford, I. D.: The electrocardiogram and disturbance of potassium metabolism. New England J. Med. **243:** 843, 1950.

[7] Eliel, L. P., Pearson, O. H., and Rawson, R. W.: Postoperative potassium deficit and metabolic alkalosis. New England J. Med. **243:** 471, 1950; **243:** 518, 1950.

[8] Engel, F. R., Martin, S. P., and Taylor, H.: On the relation of potassium to the neurological manifestations of hypocalcemic tetany. Bull. Johns Hopkins Hosp. **84:** 285, 1949.

[9] Ernstene, A. C., and Proudfit, W. L.: Differentiation of the changes in the Q-T interval in hypocalcemia and hypopotassemia. Am. Heart J. **38:** 260, 1949.

[10] Fratkin, L. B.: Potassium deficiency in surgical patients. West. J. Surg. Obst. & Gynec. **60:** 164, 1952.

[11] Furman, R. A., Hellerstein, H. K., and Startzman, V. V.: Electrocardiographic changes occurring during the course of replacement transfusions. J. Pediat. **38:** 45, 1951.

[12] Graybiel, A., and White, P. D.: Electrocardiography in practice, ed. 2. Philadelphia, Saunders, 1946.

[12a] Greenman, L., Shaler, J. B., and Danowski, T. S.: Biochemical disturbances and clinical symptoms during prolonged exchange resin therapy in congestive heart failure. Am. J. Med. **14:** 391, 1953.

[13] Grut, A., and Lund, M.: Electrocardiogram during insulin shock treatment of schizophrenia. Nord. med. **4:** 3805, 1939.

[14] Hegglin, R.: Die Klinik der energetisch-dynamischen Herzinsuffizienz. Bibliotheca Cardiologica II. Basel S. Karger, 1947.

[14a] Henderson, C. B.: Potassium and the cardiographic changes in diabetic acidosis. Brit. Heart J. **15:** 87, 1943.

[14b] Hilton, J. G.: Effects of mercurial diuresis in patients with ascites due to cirrhosis. Am. J. Med. **12:** 311, 1952.

[15] Holzmann, M.: Klinische Elektrokardiographie. Stuttgart, Thieme 1947.

[16] Howard, J. E., and Carey, R. A.: The use of potassium in therapy. J. Clin. Endocrinol. **9:** 691, 1949.

[16a] Huth, E. J., and Squires, R. D.: Cardiovascular observations in a patient with chronic hypokalemia. Program, Scientific Sessions, Twenty-Sixth Annual Meeting American Heart Association, April 9–12, 1953.

[17] Jung, R., and Jantz, H.: Über die Veranderungen des Elektrokardiogramms bei der paroxysmalen Lähmung und ihre Beziehungen zum Kaliumspiegel im Blutserum. Verhandl. deutsch. Gesellsch. Kreislaufforschg. **12:** 218, 1939.

[18] Katz, L.: Electrocardiography. Philadelphia, Lea & Febiger, 1947.

[19] Lepeschkin, E.: Das Elektrokardiogramm. Dresden und Leipzig, Theodor Steinkopff, 1942.

[20] —: Modern Electrocardiography. Baltimore, Williams & Wilkins, 1951. Vol. I.

[21] — and Surawicz, B.: The measurement of the Q-T interval of the electrocardiogram. Circulation **6:** 378, 1952.

[22] — and —: The duration of the Q-U interval and its components in electrocardiograms of normals. Am. Heart J. **46:** 9, 1953.

[22a] — and —: Unpublished observations.

[23] Levine, S. A., and Harvey, W. P.: Clinical

Auscultation of the Heart. Philadelphia, Saunders, 1949.

[23a] LEVINE, H. D., SCHWARTZ, W. B., AND RELMAN, A. S.: The electrocardiogram in potassium depletion; its relation to serum concentration and potassium balance. Program Scientific Sessions Twenty-Sixth Annual Meeting American Heart Association, April 9–12, 1953.

[24] LJUNG, O.: Zur Frage des verlängerten Q-T. Acta med. scandinav. 36: 293, 1950.

[25] —: The electrocardiogram in hypocalcemia with special reference to the T-wave. Acta med. scandinav. 136: 56, 1949.

[26] McALLEN, P. M.: The electrocardiogram associated with low levels of serum potassium. Brit. Heart J. 13: 159, 1951.

[27] MARTIN, H. E., AND WERTMAN, M.: Electrolyte changes and the electrocardiogram in diabetic acidosis. Am. Heart J. 34: 646, 1947.

[27a] METZGER, H., AND BLUM, A.: Les modifications de l'électrocardiogramme au cours de deux noveaux cas d'hypopotassemie. Definition de types d'électrocardiogrammes en fonction du taux de l'hypokalemie. Bull. et mém. Soc. méd. hôp. Paris, 23–24: 1236, 1950.

[27b] MERRIL, A. J.: The significance of the electrocardiogram in electrolyte disturbances. Am. Heart J. 43: 634, 1952.

[28] NADLER, C. S., BELLET, S., AND LANNING, M.: Influence of serum potassium and other electrolytes on the electrocardiogram in diabetic acidosis. Am. J. Med. 5: 838, 1948.

[29] NICHOLSON, W. M., AND SPAETH, W.: Some clinical manifestations of abnormal potassium metabolism. South M. J. 42: 77, 1949.

[29a] PALMER, J. H.: Isolated U wave negativity. Circulation 7: 205, 1953.

[30] PARRISH, A. E., SUGAR, S. J. N., AND FAZEKAS, J. F.: A relationship between electrocardiographic changes and hypokalemia in insulin-induced hypoglycemia. Am. Heart J. 43: 815, 1952.

[31] PEARSON, O. M., AND ELLIEL, L. P.: Post-operative alkalosis and potassium deficiency. J. Cln. Investigation 28: 803, 1949.

[32] PERELSON, H. N., AND COSBY, R. S.: The electrocardiogram in familial periodic paralysis. Am. Heart J. 37: 1126, 1949.

[33] REYNOLDS, T. B., MARTIN, H. M., AND HOMANN, R. E.: Serum electrolytes and the electrocardiogram. Am. Heart J. 42: 671, 1951.

[34] STEWART, H. J., SMITH, J. J., AND MILHORAT, A. T.: Electrocardiographic and serum potassium changes in familial periodic paralysis. Am. J. M. Sc. 199: 789, 1940.

[34a] STOLL, B., AND NISNEWITZ, S.: Electrocardiographic studies in a case of periodic paralysis. Arch. Int. Med. 67: 755, 1941.

[35] TARAIL, R.: Relation of abnormalities in concentration of serum potassium to electrocardiographic disturbances. Am. J. Med. 5: 828, 1948.

[36] THOMPSON, W. A. R.: Potassium and the T wave of the electrocardiogram. Lancet 1: 808, 1939.

[36a] WALLACE, W. W., AND MOLL, F. C.: Balance and electrocardiographic studies in a child with potassium deficiency. Pediatrics 4: 287, 1949.

[37] YU, P. N. G.: The electrocardiographic changes associated with hypercalcemia and hypocalcemia. Am. J. M. Sc. 224: 413, 1952.

Studies on the Control of Hypertension by Hyphex

II. Toxic Reactions and Side Effects

By John D. Morrow, M.D., Henry A. Schroeder, M.D., and H. Mitchell Perry, Jr., M.D.

Although effective in maintaining relatively normal levels of blood pressure in hypertensive patients and retarding some of the serious and fatal secondary consequences of the disease, hexamethonium ion and 1-hydrazinophthalazine can cause severe immediate and late reactions. The latter drug has produced collagen diseases of varying degrees of severity, all of which have regressed on cessation of medication, in 14 of 253 patients. The combination has given rise to fatal interstitial pneumonia in 5 of 89 in malignant stages of hypertension. Less serious side effects of each agent are also discussed.

THE combination of 1-hydrazinophthalazine and hexamethonium chloride has been used in the treatment of over 250 patients with hypertension for periods up to 25 months.[1] Reduction of the arterial pressure has been achieved and maintained in all with reversal of secondary effects of hypertension in a majority. Continuous administration has been required; therefore, a critical analysis of untoward reaction to these drugs is necessary to evaluate their ultimate usefulness. Reactions have been seen which seem clearly attributable to one or the other agent alone, while a few persons have exhibited an unusual response only in the presence of combined therapy.

Side Effects of Hexamethonium Ion

Hexamethonium salts in the doses employed produce a partial blockade of variable degree of all autonomic ganglia. This action leads to inhibition of many autonomic functions not concerned with reduction of pressure. Although these disturbances represent direct actions of

the drug, they must be considered "side effects." No specific sensitivities or idiosyncrasies have been encountered which were caused by hexamethonium salts. The bromide salt, used sparingly, has not led to bromidism.

Orthostatic hypotension was measurable in every case but was usually asymptomatic and decreased or disappeared with time. In patients who had previously undergone surgical sympathectomy postural fall in pressure was exaggerated and has usually required that a compromise be made in dosage in order that weakness or syncope not occur on standing. One case, R. W., a 40 year-old man exhibited a systolic drop of 100 mm. Hg and a diastolic of 60 between the supine and erect positions.

Constipation was the most troublesome complication of oral hexamethonium therapy. Suppression of intestinal motility was observed in every case; two individuals with chronic colitis were relieved of excessive frequency of stools. One noticed alternating periods of constipation and diarrhea which could not be related to laxatives or intestinal abnormality. In one, diarrhea through a canalized impaction of feces in the sigmoid colon was discovered. Constipation progressing to adynamic ileus has been seen on several occasions when inadequate attention has been given the bowel; the ileus has been reversible except when associated with organic intestinal disease (table 2).

Absorption of hexamethonium is probably altered by intestinal motility, for effects are

increased with constipation and lessened with diarrhea. For example, a 47 year old Negro woman with hypertension and nitrogen retention had been on combined therapy for four months during which time she had been severely constipated. She was admitted to the hospital with a paralytic ileus; the serum hexamethonium concentration was found to be 11.8 mg. per 100 cc. After 72 hours in the hospital without further drug therapy and before intestinal motility had been restored the level had risen to 16 mg. per 100 cc. Return of normal bowel function was followed by a prompt fall of the serum levels to normal (0.3 to 1.0 per cent). It seemed clear that the constipation in this case had led to the accumulation of a large pool of hexamethonium chloride in the gut which permitted the serum level to rise without further ingestion and despite

These were corrected by suitable lenses. Hypotonicity of the bladder was common but transient unless associated with obstruction (table 2). Decreased potency or impotence in males was constant in early stages but complete or partial recovery has been noted in many. This disturbance caused one man to discontinue therapy. No comparable changes were noticed by women.

In the presence of partial asymptomatic organic obstruction of a hollow organ, further serious obstruction has been encountered following the use of hexamethonium chloride (table 2). Prostatic obstruction has been the most frequent condition, necessitating operative interference on four occasions. Nonsuppurative otitis media has been seen in nine cases; in three, myringotomy released clear, sterile, serous exudate. The mechanism is obscure but

TABLE 1.—*Minor Unwanted Effects of Hexamethonium Chloride*

Symptoms	Frequency	Comment
Orthostatic hypotension	Every case	Decreases or disappears. Worse after surgical sympathectomy
Constipation	Every case	May disappear after 3 to 6 months
Blurring of vision	Frequent	Troublesome only in association with hypermetropia
Dryness of mouth	Very common	Usually clears in 2 to 6 weeks
Hypotonicity of bladder	Common	Only serious when organic obstruction coexists
Impotence, complete or partial	Males	Always present early—may disappear
Cold intolerance	Frequent	Warm clothes necessary

improved hydration. Three other cases with markedly elevated blood levels have been encountered[2]; all recovered. Renal insufficiency probably contributed to the retention of hexamethonium ion.[2] Constipation has been controlled by the use of stimulating laxatives at frequent intervals (at least once a day). Patients have been instructed to obtain an evacuation of the bowel at least every other day and preferably daily, thereby preventing the accumulation of excessive amounts of drug. "Urecholine" was added only rarely.

Other less serious disturbances have been noticed by most patients (table 1). Severe dryness of the mouth apparently led to alteration of taste perception; usually transient, it occurred with abrupt falls in blood pressure. Difficulties with near vision due to partial paralysis of accommodation have occurred in hypermetropic and presbyopic individuals.

in each a previous history of otitis media or sinusitis was elicited. Intestinal obstruction necessitating surgery developed in one man; many unsuspected intestinal adhesions were found, probably the result of an operation for appendicitis 16 years previously. The only fatal complication was that of parotitis in a 68 year old man with malignant hypertension complicated by nitrogen retention and recent cerebral hemiplegia. The parotitis extended into cellulitis of the neck and he succumbed to pneumonia despite intensive antibiotic therapy. This complication may be similar to the "postoperative parotitis" seen in debilitated persons.

Side Effects of 1-Hydrazinophthalazine

Minor Reactions. 1-Hydrazinophthalazine (Apresoline) is an antihistaminase in vitro; the side effects which attend its use are best

explained by the liberation of histamine. Stuffy nose, periorbital edema, lacrimation, slight but diffuse edema, headache, generalized aching and prostration were seen in a majority of patients on initiation of therapy but varied greatly in severity. A diencephalic flush similar to that induced by intracutaneous histamine was also common. The response was always self-limited and the course possibly shortened by antihistaminic drugs. All of these symptoms

exhibited severe calcific aortic stenosis. In nine other patients with angina, however, in whom a longer trial of a combination of hexamethonium and hydrazinophthalazine (Hyphex) was possible, one was partially and seven were completely relieved, while one voluntarily stopped treatment before significant change in blood pressure was obtained. One woman who had had previous admissions to hospital for neurodermatitis suffered a severe

TABLE 2.—*Obstruction of Hollow Visci Caused by Hexamethonium Chloride*

No. Cases	Previous Partial Obstruction	Viscus	Effect of Hexamethonium Ion	Treatment Necessary	Remarks
1	Intestinal adhesions, 16 yrs.	Jejunum	Complete obstruction	Operation	Recovered
1	Mesenteric root syndrome	Duodenum	Partial obstruction	Intermittent hexamethonium chloride	Recovered
1	Old peptic ulcer	Stomach	Partial obstruction	Discontinued	Recovered
2	Prostatic hypertrophy	Urethra	Complete retention of urine	Transurethral prostatectomy	Recovered
2	Prostatic hypertrophy	Urethra	Partial retention of urine	Transurethral prostatectomy	Recovered
6	Prostatic hypertrophy	Urethra	Partial retention of urine	Urecholine	Recovered
1	Prostatic hypertrophy	Urethra	Complete retention of urine	Catheterization	Recovered
1	Stricture, female	Urethra	Partial retention of urine	Catheterization	Recovered
3	Otitis media, old	Eustachian tube	Serous otitis media	Myringotomy	Recovered
6	Otitis media, old	Eustachian tube	Serous otitis media	Vasoconstrictors	Recovered
1	?	Parotid gland	Acute parotitis	Antibiotics	Died, pneumonia

Summary: Prostatic obstruction 11
Urethral obstruction 1
Intestinal obstruction 3
Eustachian tube obstruction 9
Parotid duct obstruction 1
——
Total 25
Incidence (per cent) 9.7

were milder and of shorter duration when Apresoline was used in combination with hexamethonium chloride than when Apresoline was used alone.[3] Table 3 lists the various symptoms and the treatment utilized for their control.

Serious Reactions. In nine patients immediate serious reactions occurred. In two subjects with angina pectoris Apresoline definitely caused increase in anginal pain and was discontinued after only a few doses. One of these

exacerbation of her skin eruption and therapy was stopped.

In six instances a severe febrile reaction followed the administration of Apresoline, occurring from two days to three weeks after beginning therapy. After discontinuation for several days the drug again caused abrupt febrile responses. In two women it was possible to continue the medication after one or more episodes of fever. One young woman was able to take 4-methyl 1-hydrazinophthalazine (Ba-

6130), a chemical analogue of Apresoline, without fever, but later discontinued all therapy because of lack of cooperation. In three women it has been impossible to use Apresoline, and two of these have shown a sensitivity to one or more of the analogues of Apresoline. There

of treatment which was indistinguishable from acute rheumatoid arthritis at first and, if Apresoline was continued, disseminated lupus erythematosis (7.2 per cent). The incidence is increasing. It was clearly delineated from hexamethonium intoxication, both acute, with

TABLE 3.—*List of Minor Side Effects of 1-Hydrazinophthalazine*

Effect Observed	Usual Duration Days	Treatment	Remarks
Hypertensive headache, often prostrating	2–7	Antihistamines	Less apt to occur when hexamethonium ion is given
Generalized slight edema	2–5	None	Disappears spontaneously
Coryza	2–5	None	Disappears spontaneously
Injection of conjunctivae	Many	None	No symptoms
Lassitude and weakness	2–3	None	Recurs for 1 to 3 months
Fever	1–2	None	Disappears spontaneously
Generalized aching, other "flu-like" symptoms	3–5	Antihistamines	Disappears spontaneously
Prostration	2–3	None	Disappears spontaneously
Palpitation	4–8	None	Disappears spontaneously
Slight anemia	20–60	Ferrous salts	Often disappears without treatment
Diencephalic flush	2–10	None	In neurogenic hypertension
Nausea and vomiting, anorexia	1–3	None	Disappears spontaneously
Tingling and numbness of extremities	—	Reduce dosage	On very large doses only

TABLE 4.—*Immediate Untoward Reactions to 1-Hydrazinophthalazine*

Patient	Sex	Race	Age	Type of Reaction	Measures Required	Remarks
B. K.	♀	W	48	Angina pectoris	Discontinuation	Severe angina before treatment
A. M.	♀	W	62	Angina pectoris	Discontinuation	Maintained on hexamethonium chloride alone. Calcific aortic stenosis
I. R.	♀	W	55	Severe skin eruption	Discontinuation	Maintained on hexamethonium chloride. Severe neurodermatitis previously
V. W.	♀	W	43	Fever, 3 times, prostration, "flu"	Discontinuation	Maintained on hexamethonium chloride alone
M. P.	♀	W	58	Fever twice	Temporary discontinuation	On Hyphex. No fever third time drug given
D. T.	♂	W	48	Fever, "flu," prostration	Temporary discontinuation	Maintained on small doses
H. W.	♀	W	41	Fever, "flu," prostration	Discontinuation	Maintained on hexamethonium chloride alone
E. C.	♀	W	66	Fever, "flu," prostration	Discontinuation	Maintained on hexamethonium chloride alone
E. F.	♀	W	33	Fever, "flu," prostration	Substitution of Ba-6130	Discontinued due to lack of cooperation

was no consistent history of previous allergic diseases. All but one of those exhibiting severe fever have been women (table 4).

Collagen Disease. Several patients have noticed transient arthralgia disappearing without treatment or cessation of Apresoline. In 16 a syndrome developed after 4 to 23 months

complete autonomic blockade and high drug serum level, and chronic, with interstitial pneumonia (see below). It was less well differentiated from the pyrexia occurring three days to three weeks after the initiation of hydrazinophthalazine therapy. In our experience the patients who had the most marked immediate

reactions to hydrazinophthalazine were the most likely candidates.

In no case was the diastolic blood pressure over 90 mm. Hg at the onset of the initial symptoms. Arthritis was always prominent. Often it was multiple and frequently involved the distal portions of the upper extremity.

of less than 4 million cells per cubic millimeter occurred in 5 and leukopenia of less than 3,500 cells per cubic millimeter in 4 persons of 11. Adenopathy and splenomegaly appeared in 4 patients of 13. Hyperglobulinemia of more than 2.5 Gm. per 100 cc. was present 5 times in 9 and albuminuria of a trace or more 5 times in

TABLE 5.—*Summary of Significant Findings in Acute Fatal Toxicity due to Hyphex*

Symptoms and Sign	J. J. ♂	W. J. ♂	D. M. ♂	E. M. ♀	Remarks
Age	33	49	55	52	
Race	N	N	N	N	
Malignant hypertension	Yes	Yes	Yes	Yes	Three very severe
Nitrogen in blood, (mg. per cent)	25	65	40	48	
Heart failure	Early	No	No	Severe	
Response to Hyphex	Fair	Fair	Fair	Good	
Dose, hexamethonium, (Gm. per day)	6.0	6.0	2.5	2.5	Two taking large doses
Dose, 1-hydrazinophthalazine, (Gm. per day)	0.9	1.2	0.5	0.5	Two taking large doses
Duration of treatment, (months)	4	1	2	5	
Toxic Stage					
Severe tachypnea	Yes	Yes	Yes	Yes	Worse standing, relieved lying
Duration, (days)	7	7	7	7	To death in three
Fever, (degrees C.)	39	39	38.4	37	
Venous pressure, (mm. H_2O)	120	175	165	108	
Circulation time, arm to tongue, (seconds)	20	15	13	18	
X-Ray, pulmonary congestion	Yes	Yes	Yes	—	Edema, patchy and hilar
Nitrogen in blood, (mg. per cent)	25	60	47	36	
Sodium in serum, (mEq./L.)	137	137	128	142	
Carbon dioxide combining power (mEq./L.)	17	8	24	23.5	
pH of blood, venous	7.5	7.47	—	7.43	
Urine pH	5.5	4.5	4.5	4.7	
Cause of death	?	?	?	Uremia	
Autopsy findings					
Pulmonary congestion	Yes	Yes	Yes	Yes	
Malignant sclerosis	No	Yes	Yes	Yes	
Interstitial pneumonia	Yes	Yes	Yes	Yes	

Note: An additional case occurred in a white man, age 55, with malignant hypertension, cardiac decompensation but adequate renal function. Two months after beginning therapy he developed pneumonia and died enroute to hospital. Autopsy revealed interstitial pneumonia. Two others in malignant stages with uremia died after discontinuation of Hyphex. Upon careful re-examination of sections both showed minimal signs of interstitial pneumonia.

Various skin rashes occurred in five patients. Hepatitis, demonstrated by abnormal cephalin-cholesterol flocculation, thymol turbidity, and/or hepatomegaly, appeared in 11 of 12 instances. Pyrexia over 37.5 C. was noted in 9 of 13 cases and in 3 was over 39 degrees. There was microscopic hematuria in 7 of 11 patients and in 2 the urine was grossly bloody. Anemia

11. Only one individual had all of these abnormalities, although three others had sufficient findings to suggest the diagnosis of lupus erythematosis; "L-E" cells were not found. Regression to or toward normal invariably followed cessation of the drug. In four, the arthritis was shown to be directly related to the administration of Apresoline, in that several

isolated single doses caused recurrences of high fever and acute polyarthritis after symptoms had subsided. Cortisone given to four patients relieved the arthritis rapidly. The following three cases illustrate this condition.

Case No. 1. T. P., a 56 year old white banker, first became slightly hypertensive in 1945 at the age of 48. He had suffered from vasomotor rhinitis for several years. Each year thereafter his blood pressure rose slightly until by October 1948 his systolic was 182 mm. Hg and his diastolic 114 mm. at which levels it remained. In January 1949 he suffered an attack of acute malignant hypertension with nitrogen retention and grade IV ocular fundi, which regressed with rest in bed but recurred in April. Bilateral lumbodorsal sympathectomy was performed which was successful only for 20 months. In December 1950 he experienced another attack of malignant hypertension which was reversed by Apresoline; again in March and in May, 1951 ocular fundi altered and diastolic pressure became very high. Increased doses of Apresoline appeared to cause reversal of the stage. He was started on hexamethonium chloride in September 1951 because of rising blood pressure, and achieved fairly good control (therapeutic grade 1[1]).

He continued to do well until July, 1952, when he became ill. He showed fever, hepato- and spleno-megaly, leukopenia, slight anemia, albuminuria and microscopic hematuria. These signs regressed slowly until in October arthralgia developed in his wrists and hands with objective joint changes consistent with rheumatoid arthritis. A brief course of corti-sone relieved his symptoms and he felt well until November 1952, when he was hospitalized else-where for what was believed to be hepatitis. Re-turning to St. Louis, he was found to have an en-larged liver and spleen with no jaundice. Urine revealed a few red blood cells and there was slight anemia. Retrograde pyelograms were normal. In December the nonprotein nitrogen in his blood was elevated for the first time since 1948. There was a trace of albumin and many red blood cells in his urine. Anemia had progressed but examination showed normally cellular bone marrow. He had lost 20 pounds in weight. Repeated transfusions failed to control the anemia. There was no eosino-philia, and the Hargraves test for "L-E" cells was negative on three occasions. He was normotensive. Intermittent fever as high as 39.3 C. was present, with 3,400 white blood cells and 3.1 million red blood cells per cubic millimeter. Cephalin-cholesterol flocculation was 4 plus, thymol turbidity 11.0 units. Nonprotein nitrogen in the blood was 54 mg. per 100 cc., albumin 3.8 and globulin 2.9 Gm. per 100 cc. Treatment consisted of discontinuation of Apresoline and the administration of massive doses of cortisone which have been continued to the

present. This regimen resulted in improved sense of well being, shrinking of the liver and spleen, de-crease in the nitrogen retention and control of the anemia, but there was a moderate rise in blood pres-sure partially controlled by increased doses of hexa-methonium chloride.

Case No. 2. D. T. was a 46 year old engineer who was admitted to hospital for evaluation in February 1952. He had known of hypertension for three years (first recorded systolic pressure 170
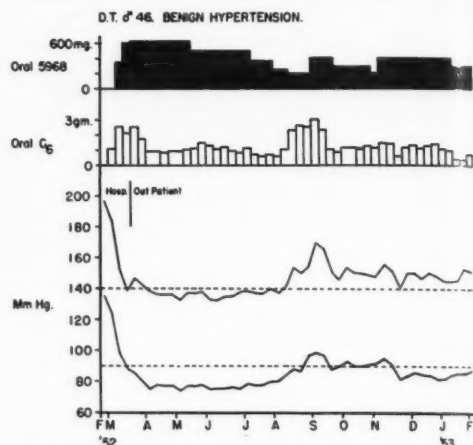
Fig. 1. Response of blood pressure to Hyphex in case 2. Each point represents the average of all measurements made during one week (approximately 35). Reduction of the dose of Apresoline (5968) was made more rapidly than the hypertensive process had regressed, and blood pressure rose. An attempt to control the rise by increased doses of hexametho-nium chloride (C_6) failed; only when those of Apreso-line were doubled did blood pressure return toward normal levels. These alterations in dosage of Apreso-line were made voluntarily by the patient, while those of hexamethonium ion were imposed by strict observance of the "self-eliminating" regimen based upon the systolic pressure at the time of each dose. The late toxic reaction first appeared in March 1953.

mm. Hg) during which time the blood pressure had gradually risen to systolic levels of 200 to 220 mm.; he had been troubled by some dyspnea on exertion and wheezing. Past history was significant in that he had "rheumatic fever" as a child and had since been told he had "leaky valves." He had been treated for anemia with iron pills and liver injections inter-mittently for three years.

Investigation revealed severe hypertension with an average systolic pressure of 200 mm. Hg and a dias-tolic of 135 mm. Hg for one week in hospital. Response was poor during an amytal sedation test.

There were no signs of cardiac decompensation and examination of the heart showed enlargement and an apical systolic murmur but no diastolic murmurs. The hemogram was normal. His kidneys concentrated the urine to a specific gravity of 1.021 and there was no albuminuria; excretion of phenol red was 20 per cent in 15 minutes. Electrocardiogram was compatible with left ventricular enlargement and myocardial damage.

Hydrazinophthalazine and hexamethonium (Hyplex) were begun in March 1952 with lowering of the pressure as shown in figure 1. For the next several months he felt well and continued to control his blood pressure, using gradually decreasing doses. In the fall of 1952 he first noticed occasional migratory joint pains and swelling of his wrists, elbows and ankles, which were never severe. In February 1953 he developed weakness, pallor and dyspnea on exertion. He was found by his physician to be anemic and he received iron and vitamin B_{12} without apparent change. On readmission, the average systolic pressure was 150 mm. and the diastolic 85. There was severe pallor and a purpuric area over the right ankle; no swelling of the joint, tenderness or deformity was present. Liver and spleen were not palpable and there was no adenopathy. Urine analysis showed 3-plus albuminuria with many red blood cells seen microscopically. The hemoglobin was 8.0 Gm. per 100 cc. with 2.7 million red cells per milliliter with normal indices. Chemical analysis revealed nonprotein nitrogen of the blood of 37 mg. per 100 cc.; total protein 6.0 Gm. per 100 cc. with albumin 3.7 Gm. and globulin 2.3 Gm. The excretion of phenol red was 12 per cent in 15 minutes. Erythroid stimulation was seen on bone marrow examination. Liver function tests showed a thymol turbidity of 8.0 units and a cephalin cholesterol flocculation of 4 plus. Antihypertensive drugs have been continued in reduced dosage.

Severe, but reversible reactions of "rheumatoid" arthritis were seen four times as illustrated by the following occurrence.

Case No. 3. B. R. was a 43 year old woman worker in a factory who was first seen in January 1952 for renal hypertension. Her systolic pressure was 180 mm. in 1945 and rose to 260 in 1950. One kidney had been removed for pyelonephritis in 1950 without effect. On examination her systolic pressure was 244 and her diastolic 130 mm. Hg. Nonprotein nitrogen in her blood was 46 mg. per 100 cc.; there was albuminuria and grade II retinopathy. She suffered a severe immediate reaction to 1-hydrazinophthalazine, which lasted several days, but her blood pressure was controlled from systolic levels of 240 and diastolic of 140 mm. Hg to normal. Control was continuous and her dosage was gradually reduced. In October 1952, she became slowly incapacitated by severe arthritis involving all the joints of her extremities. In December she was given placebos similar to 1-hydrazinophthalazine and her arthritis slowly but only partly subsided. Through an error she was given the active agent and her joints became acutely inflamed but subsided when placebos were substituted. Through a second error she received 200 mg. of Apresoline; her body temperature rose to 41 C., her joints became acutely swollen, hot and painful, and she was readmitted to hospital acutely ill. The tip of her spleen was palpable. Her blood pressure remained at normal levels, controlled by small doses of hexamethonium chloride alone, and her joints improved. On three occasions she was given Apresoline, 1-4 dihydrazinophthalazine (Ba 7441) and 1 hydrazino-4-methyl phthalazine (Ba 6130). Shortly after each, her temperature rose, her joints became acutely swollen and tender, and she became prostrated. Small doses of cortisone controlled her arthritis, her blood pressure remained at reasonable levels and she was able to return to work without taking cortisone or Apresoline.

During the acute reactions, although there was no albuminuria, hematuria, anemia or leukopenia, there was generalized lymphadenopathy and hepatomegaly. Cephalin-cholesterol flocculation was three plus and thymol turbidity 8.7 units, with serum albumin of 3.7 and globulin of 3.0 Gm. per 100 cc.

FATAL REACTIONS IN COMBINED APRESOLINE AND HEXAMETHONIUM (HYPHEX)

Interstitial Pneumonia. On combined therapy, five deaths have occurred, caused apparently by pulmonary complications. Pathologically the findings were those of interstitial pneumonia.[4]* Because of the prevalence in this series of this otherwise rare condition, the drugs are strongly suspected of being causative factors. Four of the five were in Negroes; four

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* The condition was identical pathologically with "acute interstitial fibrosis of the lungs." Four of our cases, however, differed from those of Hamman and Rich[4] and Rubin, Kahn, and Pecker,[5] in that the disease was rapidly progressive to death within a week without development of cor pulmonale. Whether a virus infection superimposed upon pulmonary dynamics altered by hexamethonium ion, chemical irritation due to Apresoline, or the interaction of both agents on pulmonary tissue caused the disease is not known. The fact that we can add five cases to the 14 previously collected[6] implicates the combination of Apresoline and hexamethonium (Hyphex) as a direct or accessory cause. The prevalence in Negroes is curious.

of the five were in men; three of the five patients who died had exhibited congestive heart failure; three of the five suffered from renal insufficiency and all had been in malignant stages of hypertension (table 5). The ratio of Negro to white patients in our series was 1:8.4; the ratio of males to females 1:1.4. The following report illustrates this condition.

Case No. 4. J. J. was a 33 year old Negro male office worker who had been discovered to have hypertension in 1943 while in the Army. After repeated determinations of his pressure, he was accepted for officers training and successfully completed two more years in the Army. He was given a routine discharge with no comment as to hypertension. In 1948 he was rejected as a Red Cross blood donor because of hypertension, but since he felt well, did not seek medical advice. In 1952 a medical examination was required to change his Civil Service status. Because of hypertension he was referred to an internist who found his blood pressure to be in excess of 220 mm. Hg systolic and 150 mm. diastolic on several occasions. Ocular fundi showed marked spasm and recent small hemorrhages. Albuminuria was also discovered for the first time.

On admission to hospital in September 1952 there was some reduction of blood pressure on bed rest to 200 mm. Hg systolic and 140 diastolic. Funduscopic examination showed no hemorrhages, exudates or papilledema. There was no evidence of cardiac failure and his general condition appeared good. A hemogram was normal. Examination of the urine confirmed the albuminuria. No growth appeared on urine culture. Intravenous pyelography showed no anatomical changes. Nonprotein nitrogen level of the blood was 25 mg. per 100 cc. Phenol red excretion was 15 per cent in 15 minutes. Radiography revealed that the heart was moderately enlarged and the lungs were clear. The electrocardiogram showed left ventricular enlargement.

Because of the markedly elevated pressure and previous observation of retinal hemorrhage this man was considered to be in a premalignant stage and therapy with Apresoline and hexamethonium (Hyphex) was begun. The initial response was disappointing and large doses of both hexamethonium chloride (4 to 6 Gm. daily) and 1-hydrazinophthalazine (1.2 Gm. daily) were required to reduce the average pressure to 160 systolic and 100 diastolic in hospital. He was continued on these doses for four months and moderately high serum levels of both agents were found. The blood pressure varied from 200 to 160 systolic and 130 to 100 diastolic.

In December 1952, he made a routine visit to the clinic and the respiratory rate was noted to be 80 per minute. He felt fairly well and aside from some difficulty in talking, he was able to carry on his usual activity. There was no evidence of cardiac decompensation and the lungs were clear on examination. Roentgenogram of the chest revealed extensive diffuse infiltration throughout both lung fields. The nonprotein nitrogen was 25 mg. per 100 cc. and the serum levels of hexamethonium chloride and 1-hydrazinophthalazine were not elevated.

The tachypnea continued and on readmission to the hospital 48 hours later his respiratory rate was 90 per minute. Body temperature was 39 C. A few fine scattered rales could be heard over both lung fields. There was no hepatomegaly or dependent edema. Slight cyanosis was present. The circulation time was 20 seconds (arm to tongue) and the venous pressure 120 mm. H_2O. On chemical analysis the serum sodium was 137 mEq. per liter, the carbon dioxide capacity, 17 mEq. per liter and the pH of venous serum, 7.5. Pulmonary ventilation was markedly increased.

Treatment consisted of nasal oxygen, rest and intensive antibiotic therapy. His respiratory rate rose steadily and on the second hospital day reached 130 per minute. Cyanosis was minimal and did not seem to be altered by oxygen therapy although the patient felt that it helped. He seemed to become exhausted and died, seven days after the onset of symptoms. Tetany was never present. Two hours before death his systolic pressure was 190 and his diastolic 130 mm. Hg.

Three other cases have been similar clinically in the rapid onset of symptoms and the downhill course lasting a week or less. In one Negro woman with severe renal damage the terminal course was gradual, consistent with that of uremia; only at autopsy was the pulmonary disturbance discovered. The only white man who developed this condition had had severe cardiac failure which had been well controlled. He was thought to suffer from acute lobar pneumonia and he died in the ambulance on the way to hospital. It is significant that in all cases observed, tachypnea and dyspnea were improved in the *supine* position.

Other Reactions. There have been five other deaths from nonhypertensive causes in patients in the malignant stage. One young Negro woman who did not control her dosage, and therefore her blood pressure, developed encephalopathy three times and lumbodorsal sympathectomy was advised. She succumbed to postoperative shock. Three have died at home of unknown causes but without recur-

rence of hypertension. As previously stated, one man developed parotitis and pneumonia from which he died.

Two deaths may be ascribed to the injudicious use of these drugs. In one young woman with encephalopathy and uremia both agents were given parenterally within a few hours of each other; a profound fall of pressure to shock levels required infusion of norepinephrine. When her blood pressure rose to previous levels after four days, pulmonary edema developed and she died. Multiple small myocardial infarcts were present at autopsy. In another hospital, placebos were substituted for the drugs after good control had been established in a case known to us. Blood pressure rose. The placebos were later replaced by full doses of the active drugs and one-half hour after the first dose the patient died suddenly. No autopsy was done.

DISCUSSION

The total incidence of fatalities in patients adequately treated with combined Apresoline and hexamethonium (Hyphex) but due to hypertensive causes (cerebral vascular accident, coronary occlusion, developing renal insufficiency) was 1.3 per cent and not caused by hypertensive complications, 7.6 per cent. Although all of the latter deaths were in patients with malignant hypertension, the gross incidence is excessive for any good therapeutic procedure. From another viewpoint, the incidence of interstitial pneumonia probably induced by therapy with Apresoline and hexamethonium (Hyphex) was 5.6 per cent in malignant hypertension (89 cases), 29.4 per cent in malignant hypertensive Negroes (17 cases), 37.5 per cent in hypertensive Negro men (8 cases) and 50 per cent in malignant hypertensive Negro men (6 cases), based on a small series. This incidence is excessive. We are at a loss to explain it. A new disease has apparently been produced by exogenous chemical agents continuously introduced into the body.

The five deaths due to nonhypertensive causes were not surprising, considering the degree of vascular damage already present.

Pneumonia following parotitis in an elderly man with renal insufficiency who had suffered complete hemiplegia, postoperative shock in a young woman with severe malignant hypertension, and sudden deaths in three patients with chronic congestive heart failure and renal insufficiency are to be expected in any series of patients with severe debilitating and fatal diseases. That they died normotensive does not necessarily implicate the drugs as causes.

More disturbing, however, is the incidence of late reactions induced by 1-hydrazinophthalazine, notably "collagen" disease with arthritis, resembling disseminated lupus erythematosus. The incidence, again, is excessive (7.2 per cent) and will undoubtedly increase. We do not believe that rheumatoid arthritis developed by chance in these individuals, for the condition was exacerbated by the drug. It represents rather, the production of a new condition by a new agent and is better explained as a phenomenon of depletion rather than as one of hypersensitivity.[2]

Because of these complications, the use of combined Apresoline and hexamethonium (Hyphex) might be restricted were it not for the almost uniformly fatal nature of malignant hypertension, to which interstitial pneumonia has been confined, and the relatively benign nature of the arthritis. The drugs incontrovertibly prolong life in malignant hypertension, and "irreversible" or fatal late reactions have occurred in only one of 97 white males. Therefore, for the present, the risk appears warranted in white persons who would otherwise deteriorate rapidly. Likewise, in all persons with severe benign hypertension no "irreversible" reaction has occurred.

The prompt appearance of fever in six cases starting therapy with 1-hydrazinophthalazine was considered a less serious reaction. Early recognition of the febrile response and appropriate reduction or omission of dosage alleviated the symptoms. Individuals developing a specific untoward reaction to 1-hydrazinophthalazine all exhibited an increased hypotensive effect. This correlation of antihypertensive activity and toxic response suggests that both may be manifestations of a single fundamental

metabolic action. In a total of 11 persons (4.2 per cent) it was considered impossible or unwise to continue 1-hydrazinophthalazine because of untoward response. In an additional four persons (1.6 per cent) who developed reactions, it was possible to continue the drug. No evidence of suppression of bone marrow activity has been discovered. The drug in combination with sympatholysis is an effective antihypertensive agent, but its use is not without hazard.

Hexamethonium salts, while good antihypertensive agents, are imperfect because of their wide range of effects resulting from diffuse autonomic blockade. In our series, all of the unwanted responses could be related to this action. Fortunately most reactions were mild, many were transient, and all cou'd be specifically treated. Serious effects of autonomic paralysis occurred only in the presence of complicating organic disease, as observed in 25 patients. In only two (0.8 per cent) was it necessary to discontinue the drug. Although methonium compounds with a longer carbon chain produce a "curariform" effect, or neuromuscular blockade, this action has not been observed with hexamethonium salts. No specific sensitivity to hexamethonium compounds was encountered, which confirms earlier observations in both animals and human beings.[5] The oral form of the drug is safe to use in the absence of uremia, provided constipation is prevented and each dose is reduced or omitted when the blood pressure is normal.[2]

Ideal drugs for use in the chronic therapy of hypertension are those whose pharmacologic action favorably affects the mechanisms of hypertension without auxiliary action or capacity for inducing hypersensitivity. Neither of these agents can be considered ideal. Hexamethonium ion causes widespread minor alteration of function not desirable for the control of hypertension, while 1-hydrazinophthalazine is capable of inducing serious late reactions.

SUMMARY AND CONCLUSIONS

Experience gained in the observation of 258 cases of hypertension treated for 6 to 25 months with combined Apresoline and hexamethonium (Hyphex) is reported with relation to the un-toward reactions encountered. Minor reactions and side effects to one or both agents were seen in most cases.

Fatal complications were observed in the form of interstitial pneumonia in five cases, uncontrolled hypotension in one and sudden death in one. 1-Hydrazinophthalazine apparently caused arthritis and "collagen-like" disease in 16, and repeated febrile responses in six. Serious obstructive phenomena due to hexamethonium chloride in previous organic obstruction occurred in 10 cases. Of the 44 cases with reactions (17 per cent), eight (3 per cent) were fatal, five due to interstitial pneumonia, one due to pneumonia following parotitis, and two due to simultaneous administration of both drugs.

In spite of reactions and side effects, the combined use of both agents is an effective and practical method of treating severe hypertension provided precautions are taken to minimize serious consequences, for the benefits observed clearly have outweighed the risks. Neither agent, however, is ideal.

ADDENDUM

Since this paper was submitted for publication, a report on the treatment of hypertension by hexamethonium ion in 39 individuals was published by Morrison.[7] Three patients with malignant hypertension, two of whom exhibited congestive heart failure and one nitrogen retention, developed bilateral pulmonary opacities and severe dyspnea, relieved in the supine position. One died and at autopsy showed pulmonary lesions not positively identified in a preliminary report but suggestive of those here considered as acute interstitial pneumonia. That this disease occurred in patients taking hexamethonium ion alone tends to incriminate this drug as the causative agent in our cases and not the combined therapy.

SUMARIO ESPAÑOL

Aunque el hexamethonium y 1-hydrazinophthalazine son efectivos en mantener presiones arteriales relativamente normales en pacientes hipertensos y retardan algunas de las consequencias serias de la enfermedad, también pueden producir reacciones serias inmedia-

tas y tardías. La última droga ha producido
enfermedades colágenas de grados variables de
intensidad, todas las cuales han tendido a
desaparecer con cesación del medicamento, en
11 de 253 pacientes. La combinación ha pro-
ducido pulmonía intersticial fatal en 5 de 89
casos de hipertensión en el estado maligno. Al-
gunos efectos no deseables menos serios de cada
droga también se discuten.

REFERENCES

1 SCHROEDER, H. A., AND MORROW, J. D.: Studies
on the control of hypertension by Hyphex. I.
Effects on blood pressure. Circulation 8: 672,
1953.

2 PERRY, H. M., JR., MORROW, J. D., AND
SCHROEDER, H. A.: Studies on the control of
hypertension by Hyphex. III. Chemical and
pharmacological observations. (To be published.)

3 SCHROEDER, H. A.: The effect of 1-hydrazino-
phthalazine in hypertension. Circulation 5: 28,
1952.

4 HAMMAN, L., AND RICH, A. R.: Acute diffuse inter-
stitial fibrosis of the lungs. Bull. Johns Hopkins
Hosp. 74: 172, 1944.

5 PATON, W. D. M., AND ZAIMIS, E. J.: The meth-
onium compounds. Pharmacol. Rev. 4: 219, 1952.

6 RUBIN, E. H., KAHN, B. S., AND PECKER, D.:
Diffuse interstitial fibrosis of the lungs. Ann.
Int. Med. 36: 827, 1952.

7 MORRISON, B.: Parenteral hexamethonium in hy-
pertension. Brit. M. J. 1: 1291, 1953.

Newer Drugs in the Treatment of Hypertension

I. Use of Hexamethonium Salts

By Homer A. Sieber, M.D., Keith S. Grimson, M.D., and Edward S. Orgain, M.D.

Fifty patients exhibiting relatively severe hypertensive vascular disease were treated with hexamethonium compounds for periods of 3 to 19 months, averaging 9 months per patient. Hexamethonium is a potent anticholinergic agent capable of lowering blood pressure for short periods. During prolonged administration, the initial effects upon blood pressure tend to become diminished or lost, so that in the long-term treatment of severe hypertension, hexamethonium therapy alone possesses limited value. Amelioration of symptoms, decrease in retinopathy and improvement in the electrocardiogram are noted. Five fatalities occurred during treatment, but none of these was attributed directly to drug action.

IN 1949, following the synthesis of a series of methonium compounds,[1] Paton and Zaimis[2] demonstrated the pentamethonium and hexamethonium halides to possess potent anticholinergic actions capable of blocking both parasympathetic and sympathetic ganglia. Of these two compounds, hexamethonium was considered superior in action, and extensive clinical trial in hypertensive disease rapidly followed. Initially hexamethonium salts were administered parenterally, but after partial gastrointestinal absorption of the drug was proven by Kay and Smith,[3] the oral route was also employed.

Utilizing both parenteral and oral methods of hexamethonium therapy, Smirk and Alstad,[4] Mackey and Shaw,[5] Fullerton and Milne,[6] Campbell, Graham and Maxwell,[7] Freis, Finnerty, Schnaper and Johnson,[8] and Johnson, Moyer, Mills and Miller[9] reported favorable results in the control of hypertension over periods up to 14 months. Tendency for the

blood pressure to return toward pretreatment levels was observed with continued administration of hexamethonium so that 5 to 10-fold increases in initial parenteral doses often became necessary to maintain original effects.

Other investigators have been much less enthusiastic. Locket, Swann and Grieve,[10] using principally oral hexamethonium bromide, reported failure of the drug to maintain lowered blood pressure over periods up to 13 weeks. Blainey,[11] employing oral and parenteral therapy, concluded that hexamethonium was ineffective in the long-term treatment of hypertension.

Serious complications have been described by Campbell and Robertson,[12] and by Bourne and Hosford.[13] Four deaths definitely attributable to hexamethonium therapy have been reported by Campbell, Graham and Maxwell,[7] Thomas and Williams,[14] Mackey and Shaw,[15] and Hirson and Kelsall.[16] Proper precautions with regard to the use of these compounds have been stressed by Grimson, Orgain, Rowe and Sieber.[17]

Although several drugs are currently available which will lower blood pressure acutely, few possess real usefulness in the long-term treatment of hypertensive disease, particularly when administered orally, a point of personal importance to patients. Because of differences of opinion concerning the practical value of hexamethonium compounds in hypertension, an investigation was begun in 1951. The pur-

pose of this paper is to present the results of prolonged hexamethonium therapy, administered principally orally, to patients suffering from severe hypertensive vascular disease. The results of combined treatment using hexamethonium and 1-hydrazinophthalazine will be reported later.

METHODS

Fifty patients exhibiting severe, stable or progressive hypertensive vascular disease with an average systolic and diastolic blood pressure of 214/128, previously unresponsive to standard medical measures, were selected for treatment. Individuals presenting mild or labile hypertensive vascular disease or primary renal disease were excluded. According to Palmer's classification of hypertension,[18] they may be grouped as follows: grade II, 24 patients; grade III, 24 patients; and grade IV, 2 patients. Their ages ranged between 31 and 62 years with an average of 48 years. There were 37 males and 13 females. Three patients had had previous sympathectomy (one Grimson, one Smithwick, and one Peet) with return of hypertension. Twenty-one patients presented one or more serious complications of hypertension prior to the onset of treatment. Cerebrovascular accidents had occurred in 12 patients and encephalopathy in 4 patients. Three patients experienced angina pectoris, 2 patients had previous myocardial infarction and 2 patients had suffered from congestive heart failure. Ten patients demonstrated slightly impaired renal function.

Of the 50 patients, 40 were hospitalized for periods of two to three weeks for institution of hexamethonium therapy. Conventional examinations were employed in the evaluation of the hypertension in each patient. These always included a thorough history, complete physical examination, routine blood counts and urine analysis, blood nonprotein nitrogen determination, two-hour phenolsulfonphthalein excretion test, teleoroentgenogram of the chest, and electrocardiogram. In most instances a Mosenthal or Fishberg concentration test, intravenous pyelograms and a Regitine[19] test for excess circulating epinephrine were obtained. During this period of observation and testing, recumbent and standing blood pressures were recorded four times daily.

Continuous hexamethonium therapy was administered by the oral route to 46 patients, and by the parenteral route to three patients. One additional patient received parenteral therapy for two months under hospital control and oral medication during outpatient care. Parenteral therapy was reserved for those patients who had significant evidence of arterial disease and moderate impairment of renal function. Treatment was continued over periods of 3 to 19 months for an average of 9 months per patient. A single exception was represented by one patient who discontinued therapy after one month because of partial ileus with distention, nausea, and vomiting.

Orally, the drug was administered on an empty stomach, at least 30 minutes before each meal and again at bedtime in order to spread the drug effect over the longest period of waking hours and to gain more uniform absorption of the drug. Recumbent and standing blood pressures were observed prior to each dose. Dosage was usually begun with 125 mg. to 250 mg. of one of the hexamethonium salts four times daily and increments of 125 mg. to 250 mg. per dose were made daily until a satisfactory blood pressure fall was obtained or until the development of distressing side effects precluded further increase. With parenteral therapy the initial dose was 2.5 mg. to 5 mg. of the hexamethonium ion every six to eight hours. Gradual increments were made each day until the desired blood pressure response was observed. Fifty mg. was considered the maximum single dose with the exception of one patient who after prolonged treatment in the hospital required 100 mg. every 4 hours to maintain the original blood pressure effect. Seldom was it possible to induce both normal recumbent and standing blood pressures because of wide variations in pressure from recumbent hypertension to symptomatic postural hypotension.

During the course of this study 13 patients received hexamethonium bromide in doses ranging from 2 Gm. to 5 Gm. daily. Five patients received hexamethonium bitartrate 3.5 Gm. to 6.3 Gm. daily, and 45 patients, hexamethonium chloride 1.0 Gm. to 4.75 Gm. daily. It should be remembered that the percentage content of hexamethonium ion in the various salts of hexamethonium is as follows: 74 per cent in hexamethonium chloride, 55 per cent in hexamethonium bromide, and 40 per cent in hexamethonium bitartrate. Simple calculation enables a change from one preparation to another without varying the hexamethonium ion given. Four patients received parenteral hexamethonium bromide in total daily doses of 15 mg. to 600 mg. of the ion.

During the early stages of this investigation, hexamethonium bromide alone was available for trial, and retention of the bromide ion made the additional use of low sodium diets hazardous. The problem was encountered only with oral therapy and was partially solved by the addition of 1.0 Gm. of ammonium chloride for each gram of the bromide salt administered. Later, when bitartrate and chloride derivatives were substituted for the bromide salt, standard low sodium diets (300 to 500 mg. sodium) were instituted almost routinely in all grade III and grade IV hypertensive patients, and in a few of the more severe grade II patients. This may have enhanced the action of the methonium compounds.

Each patient was familiarized with the side effects of the drug and given proper precautions in self-medication. The drug was reduced or omitted if faintness was noted at the time of the prescribed

dose. Cascara sagrada was advised for control of constipation; bulk laxatives were avoided. Following the patient's discharge from the hospital, blood pressures were recorded at weekly intervals by the family physician or in our outpatient clinic. More thorough examination was made once a month in the outpatient clinic, and if necessary, adjustments were advised in the dosage of hexamethonium. Every six months the renal and cardiac systems were re-evaluated by observation of the blood nonprotein nitrogen, phenolsulfonphthalein excretion test, teleoroentgenogram of the chest, and electrocardiogram.

RESULTS

Constipation, dry mouth, and blurred vision were common reactions experienced by most patients. Usually these effects diminished but seldom disappeared after prolonged drug administration. Constipation was generally well controlled by mild laxatives prescribed daily. Urecholine was employed in a few instances without evident benefit. Symptoms of paralytic ileus occurred in two patients while receiving daily doses of 1.5 Gm. of hexamethonium chloride and 2 Gm. of hexamethonium bromide respectively; each patient made an uneventful recovery after temporary discontinuance of the drug. Impotence and difficulty with urination were moderately troublesome among the male patients. By omission of one or two doses before contemplated intercourse, impotence occasionally could be avoided. One patient, while receiving large parenteral doses of hexamethonium under hospital control, developed acute urinary retention. No serious bladder difficulties were encountered in those patients receiving oral therapy.

Of the 50 patients, six stopped treatment because of disturbing side effects and of these, three presented definite problems of emotional instability.

Five deaths occurred during hexamethonium therapy, four from cerebrovascular accidents, and one from renal insufficiency with uremia. One of the patients who succumbed from a cerebrovascular accident also demonstrated progressive renal failure. Three of these patients had suffered cerebral accidents and the other two had known impairment of renal function prior to institution of treatment. No death could be attributed definitely to drug therapy. During treatment two patients ex-

perienced their first cerebral hemorrhage but recovered. Three patients developed mild congestive failure which responded to conventional therapeutic measures. One of these had exhibited heart failure previously. Four patients, three with known coronary artery disease before treatment, suffered myocardial infarction with survival in all. The average age of patients with serious complications was 49 years and the average in the fatality group was 44 years. In but a single instance, that of myocardial infarction occurring during a period of induced hypotension, was the drug thought to be directly responsible for the complication.

Effect upon Symptoms

Headaches, dizziness, dyspnea, and palpitation were diminished in most patients. Symptomatic improvement usually correlated closely with reduction in blood pressure. Several patients with only minor blood pressure response obtained relief from headaches. A few patients complained of more fatigue and weakness during treatment. Some patients complained of increased nervousness, but in others this symptom was improved. Of three patients who had associated coronary heart disease and the anginal syndrome, one noted more frequent angina pectoris in association with postural hypotension.

Effect upon Blood Pressure

Excessive hypotensive responses frequently were noted upon initiation of hexamethonium therapy and considerable caution was demanded to prevent overdosage. The drug effects were always greater upon systolic than diastolic pressure and greater on standing than recumbent pressure. With three exceptions a recumbent diastolic pressure of 100 mm. Hg or less was not maintained beyond one or two months of treatment. In this series, age apparently was not a determining factor in the blood pressure response.

Table 1 presents the effect upon blood pressure of continuous administration of the hexamethonium compounds over prolonged periods. The pretreatment blood pressure figures represent an average of numerous readings recorded from each patient during the months prior to

and during hospitalization. With treatment, the blood pressure response is divided into three periods: (1) while ambulatory in the hospital; (2) during the first four months of outpatient care, and (3) during the period of late outpatient care ranging from 5 to 19 months (average 10.6 months). For purposes of classifying the response of blood pressure to treatment, the patients are divided arbitrarily into three groups for each treatment period.

reduction in blood pressure but must be considered to be "poorly or inadequately" controlled by hexamethonium as judged from effects upon recumbent pressure.

Hexamethonium therapy was initiated in 40 patients while under observation in the hospital. Ten additional patients were started on treatment in the outpatient clinic so that a total of 50 patients were observed during the first four months of outpatient care. Thirty-

TABLE 1.—*Effect upon Blood Pressure*

Grade	Average Age		Average BP Before Treatment	Hospital 40 patients			During First 4 Months 50 patients			5–19 Months 37 patients		
				Group A	Group B	Group C	Group A	Group B	Group C	Group A	Group B	Group C
II	48	Recumbent	202/124	9*	2	4	6	4	14	1	9	7
		Standing	182/122	13	0	2	9	8	7	5	8	4
III	49	Recumbent	220/132	6	6	11	1	6	17	1	3	14
		Standing	195/126	17	4	2	7	6	11	5	4	9
IV	34	Recumbent	216/138	1	1	0	1	0	1	1	0	1
		Standing	181/130	2	0	0	2	0	0	1	0	1
Total		Recumbent		16	9	15	8	10	32	3	12	22
		Standing		32	4	4	18	14	18	11	12	14

* Numerals refer to number of patients.

Group A includes those patients whose average blood pressure fell to 160/110 or less; group B comprises those patients whose average blood pressure fell to 180/115 or less; and group C contains those patients whose average blood pressure response failed to reach the latter level. Although both recumbent and standing blood pressure averages are recorded in this classification, the effect upon recumbent blood pressure alone is used for interpretation of results. A survey of master blood pressure charts maintained for each patient reveals that those patients whose recumbent blood pressure response was classified in group A exhibited "good" control of pressure by drug therapy. Similarly, those patients included in group B manifested only "fair" control of pressure. Patients in group C demonstrated variable

seven patients continued therapy from 5 to 19 months (average 10.6 months). Thirteen patients, seven grade II and six grade III, of the original group treated are not included in the late follow-up period. In eight of these blood pressure was poorly controlled and drug therapy was either discontinued or altered by the addition of other drugs. The remaining five patients exhibited variable control of blood pressure, but treatment was discontinued because of undesirable side effects in two, an essentially normal level of pressure following myocardial infarction in one, and excessive postural hypotension in one; the fifth patient was lost from follow-up.

Among those patients with hypertension of grade II severity good blood pressure control was maintained during the three treatment

periods as follows: 9 of 15 during hospitalization, 6 of 24 during the first four months of outpatient care, and 1 of 17 during the late period of follow-up. For these same three treatment periods, good control was observed in the patients exhibiting grade III hypertension as follows: 6 of 23, 1 of 24, and 1 of 18. Of the two patients with grade IV hypertension, one did well during hospitalization but not subsequently. The second patient exhibited only fair control during hospitalization,

TABLE 2.—*Effect upon Hypertensive Retinopathy**

Classification	Before Treatment	During Treatment				
		I	II	III	IV	No Follow-up
Grade I	4†	4	0	0	0	0
Grade II ...	28	0	23	2	0	3
Grade III ..	16	0	9	4	1	2
Grade IV...	2	0	1	1	0	0
Totals....	50	4	33	7	1	5

* Retinopathy graded according to Keith-Wagener classification.

† Numerals refer to number of patients.

but during the subsequent nine months of outpatient care, blood pressure was well controlled at almost normal levels.

It should be noted that better results were recorded in the grade II than in the grade III hypertensives. Return of blood pressure toward or to levels preceding treatment developed in 32 of 50 patients during the first four months and in 22 of 37 patients during the subsequent period. The number of satisfactory responses decreased as time passed in spite of regular increments of hexamethonium to each patient's maximum tolerated dose. The total results for all patients treated reveal that good blood pressure control was observed in 16 patients (40 per cent) during hospitalization, in 8 patients (16 per cent) during early outpatient care, and only in 3 patients (6 per cent of the original group) during the late follow-up period. Postural lowering of blood pressure was better maintained (32, 18, and 11 patients

for comparable periods), but the value of such an effect upon the hypertensive process is not yet known.

Among those patients with good control of pressure (group A), low sodium diets were employed concurrently in the three treatment periods as follows: six patients during hospitalization, one during the first four months, and two during the late follow-up period.*

Effect upon Retinopathy

Table 2 presents the number of patients with each degree of hypertensive retinopathy initially, and shows the subsequent changes after completion of follow-up periods of 3 to 19 months. Of 45 patients followed personally, three exhibited progressive retinal changes, two from grade II to grade III, and one from grade III to grade IV retinopathy. Blood pressure was inadequately controlled in these three, and each was classified in group C.

Eleven patients showed regression of retinopathy: nine from grade III to grade II, one from grade IV to grade III, and one from grade IV to grade II. Of this group blood pressure control was inadequate in five, fair in two, and good in four. It is of interest that changes in the optic fundi may regress even though blood pressure is but partially controlled. In the remaining 31 patients, retinopathy remained unchanged.

One of 3 who showed progression, 8 of 11 who showed regression, and 12 of 31 who had unchanged retinopathy followed low-sodium diets.

Effect upon Electrocardiogram

Table 3 presents the electrocardiographic changes before and after 6 to 12 months of treatment. Thirty-one patients initially showed the well-recognized S-T segment and T-wave changes associated with hypertension, and 26 of these had follow-up electrocardiograms.

* Group B patients who received low sodium diets were as follows: 4 of 9 patients in the hospital, 4 of 10 patients during the first four months, and 3 of 12 patients during the late follow-up period. Group C patients using low sodium diets during the same three treatment periods were as follows: 10 of 15, 16 of 32 and 10 of 22.

Seven patients demonstrated reversion of their S-T segment and T-wave abnormalities to normal. Of these seven, six had good blood pressure control and the seventh was classified as inadequate blood pressure control in spite of some reduction in pressure. None of the patients with "left ventricular strain" pattern exhibited a significant increase in these changes, and no patient with an initially normal electrocardiogram developed the "strain" pattern. In no instance was left axis

TABLE 3.—*Effect upon Electrocardiogram*

ECG	Before Treatment	During Treatment			
		Normal	L A D only	"L V S"	No follow-up ECG
Normal.........	14*	10	0	0	4
Left Axis Deviation only....	5	0	3	0	2
"Left Ventricular strain" pattern.......	31	5	2	20	4
Totals........	50	15	5	20	10

* Numerals refer to number of patients.

deviation converted to a normal electrical axis. Two of the 7 patients whose electrocardiograms reverted to normal and 11 of the remaining 19 patients followed who retained the "strain" pattern were given salt-restricted diets.

Effect upon Heart Size

Detailed measurements of the cardiac shadow on films and adjustment according to weight and height by use of the Ungerleider Chart[20] permitted calculation of percentage of deviation from average normal heart size. Patients grouped in table 4 as having moderately enlarged hearts had a percentage deviation from normal of plus 11 to 20 per cent. Those grouped as having markedly enlarged hearts had a deviation of plus 20 per cent or more. All follow-up teleoroentgenograms were made after at least six months of treatment.

The hearts of five patients, initially normal

in size, showed progressive enlargement. Only in one of these was good blood pressure control observed, and there was no evidence of heart failure or myocardial infarction to explain the increased heart size. Low sodium diets were utilized in three patients of this group.

In two patients with moderately enlarged hearts initially, a decrease in heart size to within normal limits accompanied a reduction in blood pressure to near normal levels. Salt restriction was employed in the diets of both patients.

TABLE 4.—*Effect upon Heart Size*

Heart Size	Before Treatment	During Treatment			
		Normal	Moderate Enlargement	Marked Enlargement	No Follow-up X-ray
Normal.........	38*	30	4	1	3
Moderate Enlargement....	7	2	3	0	2
Marked Enlargement....	5	0	0	5	0
Totals........	50	32	7	6	5

* Numerals refer to number of patients.

Of five patients with marked cardiac enlargement before hexamethonium therapy, three showed no significant change in heart size; two showed a slight increase in heart size, one occurring with left ventricular failure, and the other following myocardial infarction. Two of these patients had fair blood pressure control, but the remaining three exhibited no significant lowering of blood pressure. Three of these patients, including the two with increasing heart size, followed low sodium diets.

Effect upon Renal Function

Before initiating therapy and at regular intervals thereafter, renal pathology and function were determined by conventional examinations. Intravenous pyelograms revealed only a few minor abnormalities.

Thirteen patients had mild to moderate albuminuria which disappeared during treatment in five. Three patients developed mild

proteinuria. Of 40 patients with normal renal function initially, 3 developed slight impairment of function as evidenced by well-controlled phenolsulfonphthalein tests. Two of 10 patients with impaired renal function showed progressive renal damage and death. One died of uremia in the thirteenth month of treatment; the other succumbed during acute hypertensive encephalopathy after four months of treatment. In the former patient, a check of renal function made three months prior to death revealed no progression in previously impaired renal function.

DISCUSSION

Hexamethonium is a powerful anticholinergic compound capable of lowering blood pressure in most patients during initial periods of therapy. No significant differences in potency were noted among the three halide salts employed when dosages were compared according to content of hexamethonium ion. The oral bromide salt, however, provided the constant hazard of bromism, and in two patients, elevation of blood bromide concentration above 200 mg. per 100 cc. demanded discontinuance of the drug. Reduction in pressure may be maintained for periods varying from four to eight months after which the initial blood pressure control is occasionally maintained but usually becomes diminished or lost. Partial relief from the side reactions of the drug also occurs, but these side effects often remain sufficiently troublesome to prevent further increase in drug dosage when additional blood pressure effect is desired. This was observed in the four patients receiving parenteral hexamethonium as well as those treated with the oral preparation. The three postsympathectomy patients proved unusually sensitive to the postural hypotensive effects of the drug and were able to maintain a more satisfactory blood pressure response with continued therapy. Postural hypotension represents the most frequent and troublesome action of the drug and commonly prevents dosage adequate for good recumbent effect. In only three patients was it possible to maintain a recumbent diastolic pressure of 100 mm. Hg or less beyond two months.

Relief from hypertensive symptoms occurred in many, and surprisingly enough, in a few patients as hypertension returned, headaches remained absent or diminished. Decrease in retinopathy and improvement in the electrocardiogram occurred in a few patients. Heart size and renal function were not significantly affected by drug therapy. In some patients, progression of hypertension seemed temporarily retarded and in a few, life expectancy appeared definitely increased.

Fewer complications and better therapeutic results were recorded for patients in the grade II hypertensive group than for those classified as grade III. Neither age nor the duration of hypertension prior to initiation of therapy appeared to be determining factors in the treatment response. Dramatic reduction in blood pressure and regression of retinopathy were observed in two patients with malignant hypertension, one of whom received the bromide derivative and a normal sodium chloride intake.

The concurrent employment of low sodium diets may have enhanced individual blood pressure responses but apparently has not altered significantly the results of long-term drug therapy in this series.

No deaths attributable to hexamethonium therapy were encountered. Of many major complications observed during the course of this study, only one can be directly related to drug effect. This patient, previously diagnosed as having coronary heart disease and myocardial infarction, suffered a second myocardial infarction during a period of excessive drug-induced hypotension. The incidence of complications in this series appears to reflect the severity of the disease treated rather than a deleterious effect of the drug utilized. However, because of the many immeasurable factors involved, it is impossible to exonerate the drug completely as a contributing force to the complications.

Hexamethonium compounds are a valuable addition to the armamentarium of drugs in the treatment of hypertension when blood pressure control is urgent or desirable for limited periods. For this purpose it is very probably the best single drug available today. Oral administration, even though drug absorption from the gut is variable, appears feasible

for the usual patient, but in the acute hypertensive state with cerebral, cardiac or renal complications, the parenteral route affords a more evenly controlled blood pressure and is preferred. Our results with prolonged oral and parenteral therapy have not been satisfactory. The hexamethonium compounds when used alone appear to possess limited value in the long-term treatment of severe hypertensive vascular disease. The effect on mild or labile hypertension was not tested owing to difficulty in evaluation of treatment results.

Coronary artery disease, encephalopathy, fresh or old cerebral thrombosis, or renal insufficiency present potential hazards to the use of methonium compounds. When blocking agents of this type are considered for blood pressure control, extreme caution must be observed.

SUMMARY

1. Fifty patients exhibiting relatively severe, stable or progressive hypertension were treated with hexamethonium compounds over periods of 3 to 19 months for an average of 9 months per patient.

2. Good control of blood pressure by hexamethonium as evidenced by average recumbent blood pressure levels of 160/110 or less was recorded for three treatment periods as follows: (1) during hospitalization, 16 patients (40 per cent); (2) during first four months of outpatient care, 8 patients (16 per cent); (3) during the subsequent 5 to 19 months, 3 patients (6 per cent). Postural changes in blood pressure were uniformly greater.

3. Hexamethonium is a potent anticholinergic agent capable of lowering blood pressure for short periods. During prolonged administration the initial effects upon blood pressure tend to become diminished or lost, so that in the long-term treatment of severe hypertension, hexamethonium therapy alone possesses limited value.

4. Frequent amelioration of hypertensive symptoms and occasional decrease in retinopathy and improvement in the electrocardiogram are noted. Heart size and renal function have not been altered significantly.

5. Five deaths occurred during the treatment period, but in no instance was the fatality attributed directly to drug action. In addition many serious complications were observed, but these, with one exception, appear to reflect the severity of the hypertensive disease rather than a deleterious effect of the drug itself.

Sumario Español

Cincuenta pacientes exhibiendo enfermedad hipertenso vascular relativamente severa fueron tratados con compuestos de hexamethonium por períodos de 3 a 19 meses, con un promedio de 9 meses por paciente. El hexamethonium es un agente anticolinérgico potente capaz de disminuir la presión arterial por períodos cortos. Durante la administración prolongada, los efectos en la presión arterial disminuyen o desaparecen, de manera que en el tratamiento a lo largo de la hipertensión el hexamethonium solamente tiene un valor limitado. Mejoraminto de síntomas, disminución en retinopatía y mejoramiento en el electrocardiograma se observaron. Cinco fatalidades ocurrieron durante el tratamiento, pero ninguna fué atribuible a la acción directa de la droga.

REFERENCES

[1] BARLOW, R. B., AND ING, H. R.: Curare-like action of polymethylene bis-quaternary ammonium salts. Brit. J. Pharmacol. 3: 298, 1948.

[2] PATON, W. D. M., AND ZAIMIS, E. J.: The pharmacological actions of polymethylene bistrimethylammonium salts. Brit. J. Pharmacol. 4: 381, 1949.

[3] KAY, A. W., AND SMITH, A. N.: Effect of oral hexamethonium salts on gastric secretion. Brit. M. J. 2: 807, 1950.

[4] SMIRK, F. H., AND ALSTAD, K. S.: Treatment of arterial hypertension by penta- and hexamethonium salts. Brit. M. J. 1: 1217, 1951.

[5] MACKEY, W. A., AND SHAW, G. B.: Oral hexamethonium bromide in essential hypertension. Brit. M. J. 2: 259, 1951.

[6] FULLERTON, C. W., AND MILNE, I. G.: The hexamethonium compounds in the treatment of hypertension. Canad. M. A. J. 65: 302, 1951.

[7] CAMPBELL, A. J. M., Graham, J. G., AND MAXWELL, R. D. H.: Treatment of hypertension by oral methonium compounds. Brit. M. J. 1: 251, 1952.

[8] FREIS, E. D., FINNERTY, F. A., JR., SCHNAPER, H. W., AND JOHNSON, R. L.: The treatment of hypertension with hexamethonium. Circulation 5: 20, 1952.

[9] JOHNSON, I., MOYER, J. H., MILLS, L. C., AND

MILLER, S. I.: Treatment of hypertension: Results with hexamethonium salts administered orally. Texas J. Med. **48**: 331, 1952.

[10] LOCKET, S., SWANN, P. G., AND GRIEVE, W. S. M.: Methonium compounds in the treatment of hypertension. Brit. M. J. **1**: 778, 1951.

[11] BLAINEY, J. D.: Hexamethonium compounds in the treatment of hypertension. Lancet **1**: 993, 1952.

[12] CAMPBELL, A., AND ROBERTSON, E.: Treatment of severe hypertension with hexamethonium bromide. Brit. M. J. **2**: 804, 1950.

[13] BOURNE, G., AND HOSFORD, J.: Letters to the Editor: Methonium compounds in hypertension. Lancet **1**: 527, 1951.

[14] THOMAS, O. M., AND WILLIAMS, R. G.: Correspondence: Paralytic ileus after hexamethonium. Brit. M. J. **1**: 1331, 1951.

[15] MACKEY, W. A., AND SHAW, G. B.: Correspondence: Paralytic ileus after hexamethonium. Brit. M. J. **1**: 1205, 1951.

[16] HIRSON, C., AND KELSALL, A. R.: Letters to the Editor: Methonium compounds in hypertension. Lancet **1**: 585, 1951.

[17] GRIMSON, K. S., ORGAIN, E. S., ROWE, C. R., JR., AND SIEBER, H. A.: Caution with regard to use of hexamethonium and "Apresoline." J. A. M. A. **149**: 215, 1952.

[18] PALMER, R. S., LOOFBOUROW, D., AND DOERING, C. R.: Prognosis in essential hypertension. New England J. Med. **239**: 990, 1948.

[19] EMLET, J. R., GRIMSON, K. S., BELL, D. M., AND ORGAIN, E. S.: Use of Piperoxan and Regitine as routine tests in patients with hypertension. J. A. M. A. **146**: 1383, 1951.

[20] UNGERLEIDER, H. E., AND GUBNER, R.: Evaluation of heart size measurements. Am. Heart J. **24**: 494, 1942.

Problems in the Diagnosis and Surgical Treatment of Pulmonic Stenosis with Intact Ventricular Septum

By John W. Kirklin, M.D., Daniel C. Connolly, M.D., F. Henry Ellis, Jr., M.D., Howard B. Burchell, M.D., Jesse E. Edwards, M.D., and Earl H. Wood, M.D.

Obstruction to pulmonary blood flow may occur in the pulmonic valve, in the infundibulum or in both. Cardiac catheterization aids in the determination of the site of obstruction. Criteria for the differentiation at operation of valvular and infundibular pulmonic stenosis are enumerated, and the usefulness of accurate pressure tracings during operation is emphasized. The accurate identification of the site or sites of obstruction to pulmonary blood flow is essential to proper surgical management. A correctly selected operation must be carried out in as complete a manner as possible.

ONE of the significant contributions to the treatment of congenital heart disease has been the introduction of pulmonic valvotomy by Sellors[1] and its extension by Brock,[2] Blalock and Kieffer,[3] Potts and associates[4] and others. Nonetheless, certain problems remain in the surgical management of congenital pulmonic stenosis with intact ventricular septum.

The results of pulmonic valvotomy for the treatment of pulmonic stenosis with intact ventricular septum must depend upon two factors. First, they are related to the anatomic details of the pulmonic obstruction existing in a given case. Thus, if there is valvular pulmonic stenosis alone, one may anticipate a good result from a properly executed procedure. If on the contrary, there is some degree of obstruction produced by the configuration of the outflow tract of the right ventricle below the valve, there may be a less satisfactory result from the operation. Secondly, the extent of the opening which the operation produces in the stenotic pulmonic valve must directly influence the result of the procedure; that is, if the valve is incompletely opened, there may be a less satisfactory reduction in right ventricular pressure than if a complete opening of the valve is attained.

Unfortunately, in spite of the considerable literature now available upon this subject, it is somewhat difficult to obtain accurate information concerning the changes in right ventricular pressure which have been obtained by operation. The available literature on this matter, however, is summarized and discussed in conjunction with a discussion of the results in our group of cases. Furthermore, the anatomic details of the obstruction to pulmonary blood flow are not always clearly elucidated in the necropsy reports of the cases in the literature; however, these reports are reviewed and will be discussed in conjunction with a review of our own anatomic studies.

Anatomy of the Obstruction to Pulmonary Blood Flow

Pulmonic stenosis with intact ventricular septum may be the only anatomic defect present or it may be associated with an atrial septal defect or a patent foramen ovale.

There are basically three types of obstruction to pulmonary blood flow. The pathologic picture of pure valvular stenosis is strikingly constant. The pulmonic valves are fused and form a dome-shaped or conical diaphragm with a central aperture of variable size. In the second type, there is obstruction to pulmonary blood flow in the outflow tract or infundibulum of the right ventricle in the presence of a normal pulmonic valve. This obstruction may consist of a diffuse narrowing of the infundibulum or of a point of localized stenosis located in the

outflow tract at either a high, intermediate or low position. A third type of obstruction may exist in which there is a combination of a stenotic valve and an infundibular stenosis.

The literature was reviewed in an attempt to tabulate the necropsied cases of pulmonic

localized stenotic area in the subpulmonic region was the only defect present.

To investigate further the nature of the obstruction to pulmonary blood flow in cases of pulmonic stenosis with intact ventricular septum, six hearts in our collection exhibiting

TABLE 1.—*Necropsied Cases of Pulmonic Stenosis With Intact Ventricular Septum*
(Review of Literature)

Defect	Cases	Valvular stenosis	Infundibular stenosis	Valvular and infundibular stenosis
Pulmonic stenosis with patent foramen ovale....	57 (42%)*	47 (83%)†	3 (5%)†	7 (12%)†
Pulmonic stenosis with intact atrial septum.....	80 (58%)*	55 (69%)‡	17 (21%)‡	8 (10%)‡
Total....................................	137	102 (74%)*	20 (15%)*	15 (11%)*

* Per cent of 137.   † Per cent of 57.   ‡ Per cent of 80.

TABLE 2.—*Pulmonic Stenosis With Intact Ventricular Septum, Necropsy Series (Mayo Clinic)*

Age	Sex	Foramen ovale	Pulmonic valve orifice, mm.	Infundibulum	Cause of death
3 mo.	F	Probe-patent	3	Marked narrowing	Congestive failure
60 yr.	F	Closed	7	No narrowing	Congestive failure
53 yr.	M	Probe-patent	9	No narrowing	Carcinoma of kidney; *Staphylococcus aureus* septicemia.
26 yr.	M	Probe-patent	5	Marked narrowing	Cerebral abscess
3½ yr. (case 6)	F	Open; short valve of foramen ovale; perforation of valve	1.5	Slight narrowing	Postoperative
22 yr. (case 9)	M	Probe-patent	5	Marked narrowing	Postoperative

stenosis with intact ventricular septum with reference to the site and nature of the obstruction to pulmonary blood flow.[5-34] Only cases in which adequate postmortem data were available were included. Detailed information, particularly relative to cases with infundibular stenosis, was frequently lacking. One hundred and thirty-seven cases with adequate data were found and are summarized in table 1. The infundibular stenosis was usually described as a narrowing of the outflow tract of the right ventricle or infundibulum, but in 11 cases, a

this defect were re-examined (table 2). Of the six hearts available for examination, all showed marked pulmonic valvular stenosis, the pulmonic valve opening varying from 1.5 to 9 mm. in diameter. Infundibular stenosis without valvular stenosis was not encountered in this series.

Because our observations differ from published reports referred to above and because the anatomic features of the outflow tract may be of importance in the surgical management of these cases and the results to be expected, a

short discussion of the anatomic features of this area is warranted. In the right outflow tract of the normal heart there are two recognizable bundles of muscle which together form the shape of an inverted "V." One bundle extends

FIG. 1. Pulmonary valve and outflow portion of right ventricle in a normal heart. The anterior wall of the right ventricle has been incised parallel with the ventricular septum and deflected to the right (left side of illustration). From beneath the pulmonic valve two muscle bundles diverge, one of which (1) is the crista supraventricularis. The second (2) extends from the base of the pulmonic valve to the ventricular septum. In its inferior aspect this bundle continues to the anterior wall of the right ventricle as the moderator band. A set of chordae from the medial leaflet of the tricuspid valve insert into a specialized papillary muscle of the second bundle. This attachment is seen to left of the 2 in the illustration.

from under the pulmonic valve downward and to the right to join the anterior wall of the right ventricle and is frequently referred to as the crista supraventricularis. The other limb of the inverted "V" extends from under the pulmonic valve down along the ventricular septum. Chordae from the medial portion of the anterior tricuspid leaflet insert into this mass of muscle (fig. 1).

In the six hearts examined there was marked

hypertrophy of the muscle of the right ventricle and particularly of the two bundles of muscle described in the preceding paragraph. In four of the six hearts, this hypertrophy was sufficient to produce significant narrowing of the outflow tract. This finding is in contrast to the scattered incomplete reports of infundibular stenosis in association with pulmonic valvular stenosis

FIG. 2. Pulmonic stenosis with intact ventricular septum (case 6). Note the diffuse narrowing of the outflow tract in addition to the stenotic pulmonary valve.

encountered in the literature. Undoubtedly, the attention of examiners is drawn primarily to the startling appearance of the pulmonic valve itself, and the anatomic features of the outflow tract are easily overlooked.

Two types of narrowing were seen in the four hearts exhibiting infundibular stenosis. One type is a diffuse narrowing of this region and is portrayed in figure 2 (case 6). Two hearts showed a definitely localized area of stenosis formed mainly by the two hypertrophied muscle bundles described previously. There was slight dilatation beyond the area of stenosis, the dilated portion being represented by the pulmonary valve inferior to the stenotic ostium in one case (fig. 3). Case 9 demonstrated a similar situation with the point of maximal stenosis occurring lower in the outflow tract, 2.3

cm. below the valve orifice (fig. 4). The in-
fundibular stenosis encountered in the presence
of valvular stenosis described previously may
be considered as being due to the muscular

FIG. 3. Combination of valvular and infundibular
stenosis. Note the localized area of stenosis in the
outflow tract just inferior to the valve.

FIG. 4. Valvular and infundibular stenosis
(case 9). A localized area of infundibular stenosis is
present 2.3 cm. below the stenotic pulmonary valve.

hypertrophy associated with the valvular
stenosis.

The surgical implications of these anatomic
findings are significant. Division and dilatation
of the stenotic valve in a case such as illustrated
in figure 5, where the outflow tract is not nar-
rowed, should produce a good physiologic
result. On the other hand, where significant
infundibular narrowing exists in association
with valvular stenosis, simple division of the

valve alone results in improvement, but right
ventricular pressures may remain relatively
elevated. In considering a further attack on
the stenotic area in the infundibulum, the fact
that the chordae from the medial portion of
the anterior leaflet of the tricuspid valve cross
the outflow tract and insert in the hypertro-
phied muscle bundle along the ventricular
septum must be remembered. Injury to this
structure could result in tricuspid insufficiency

FIG. 5. Pulmonic valvular stenosis. The outflow
tract of the right ventricle is wide in this instance.

PHYSIOLOGIC DEMONSTRATION OF VARIATION
IN SITES OF OBSTRUCTION

Pulmonic stenosis can be diagnosed at car-
diac catheterization by the demonstration of a
high systolic pressure in the right ventricle
and a low systolic pressure in the pulmonary
artery.

Roentgenoscopic observation of the catheter
tip, together with continuous monitoring of
the pressure being transmitted through the
catheter, enables one to localize the region in
the cardiac shadow at which the change occurs
from high right ventricular pressure to low
pulmonary arterial pressure. Under ideal cir-
cumstances, one can determine whether this
change occurs abruptly in the region of the
pulmonic valve or whether it is first detected
at a position in the outflow tract of the ven-
tricle, some distance proximal to the valve.

If an abrupt change in systolic pressure can

be demonstrated with certainty to occur at the valve, it is an indication that a valvular type of stenosis exists (figs. 6 and 7). In cases of infundibular stenosis, it is frequently possible by careful manipulation of the catheter during its withdrawal from the pulmonary artery to detect an intermediate zone of pressure in the outflow tract of the right ventricle. This finding is characteristic of infundibular pulmonic stenosis (figs. 6 and 7).

DIAGRAMMATIC REPRESENTATION OF DIFFERENT TYPES OF PULMONIC STENOSIS AND ASSOCIATED PRESSURE RECORDINGS DURING SLOW WITHDRAWAL OF CATHETER TIP THROUGH AREA OF STENOSIS
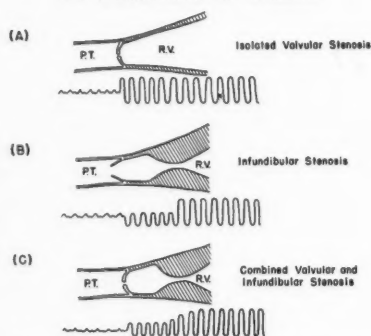
Fig. 6. Schematic representation of different types of pulmonic stenosis and associated pressure recordings that might be obtained during slow withdrawal of tip of catheter through stenotic region. (A) Valvular stenosis; (B) infundibular stenosis with normal valve; (C) combined valvular and infundibular stenosis. The type of pressure recording theoretically expected on withdrawal of the catheter from pulmonary artery to right ventricle is seen under each diagram.

In figure 6, the three types of obstruction to pulmonary blood flow are diagramed, together with the types of pressure tracing theoretically expected. In the upper diagram, the stenosis exists solely at the valve, and, on withdrawal of the catheter, an abrupt change from low systolic pulmonary arterial pressure to the typically high systolic ventricular pressure is obtained, no matter how slowly the withdrawal is carried out. In the middle diagram, the stenosis exists in the outflow tract of the right ventricle and the pulmonic valve itself is normal. Under such circumstances, when the catheter is withdrawn slowly from the pulmonary artery to the right ventricle, an

intermediate zone of pressure may be detected in the region of the outflow tract of the ventricle. The intermediate zone is characterized by a low systolic pressure equal to pulmonary arterial systolic pressure and a low diastolic
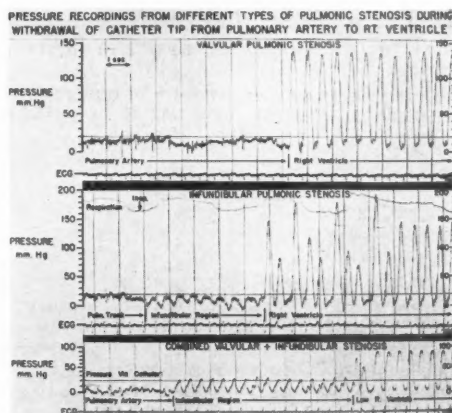
Fig. 7. Pressure tracings from different types of pulmonic stenosis recorded during withdrawal of catheter tip from pulmonary artery to right ventricle, during routine cardiac catheterization. The first panel shows the abrupt change in pressure occurring at the valve in a patient with valvular pulmonic stenosis and atrial septal defect (case 6). The second panel shows the zone of pressure detected on withdrawal of the catheter from pulmonary artery to right ventricle in a patient (case 4) with infundibular stenosis without valvular stenosis. This intermediate zone of pressure is characterized by systolic pressure equal to that of the pulmonary artery and a diastolic pressure equal to that of the right ventricle. The bottom panel shows the zone of intermediate pressure detected on withdrawal of the catheter from pulmonary artery to right ventricle in a patient with combined valvular and infundibular stenosis and ventricular septal defect (not included in the present series of patients). In this instance an abrupt rise of pressure is evident immediately below the valve, indicating the presence of a valvular stenosis. However, a further rise in pressure is observed on withdrawal of the catheter tip into the low right ventricle, indicating the additional presence of subvalvular stenosis.

pressure equal to the right ventricular diastolic pressure in contrast to the higher diastolic pressure in the pulmonary trunk. In the lowermost diagram of figure 6, an obstruction is present in the outflow tract of the right ventricle, but, in addition, a valvular pulmonic stenosis is present. Under such circumstances,

a low pressure exists beyond the stenosed pulmonic valve and an intermediate zone of pressure exists in the infundibular region; however, under these conditions, the systolic pressure in the infundibular region will exceed that in the pulmonary artery. The actual pressure tracings from patients with these different types of stenosis are shown in figure 7.

TYPES OF PULMONIC STENOSIS IN WHICH NO
INTERMEDIATE PRESSURE ZONE MAY BE DETECTED AT
CARDIAC CATHETERIZATION

(1)   P.T.   R.V.   Isolated Valvular Stenosis

(2)   P.T.   R.V.   Valvular Stenosis with a mild degree of Infundibular Stenosis

(3)   P.T.   R.V.   Normal Pulmonic valve, with localised Infundibular Stenosis close to valve

Type of pressure tracing during slow withdrawal of catheter tip through Stenosis
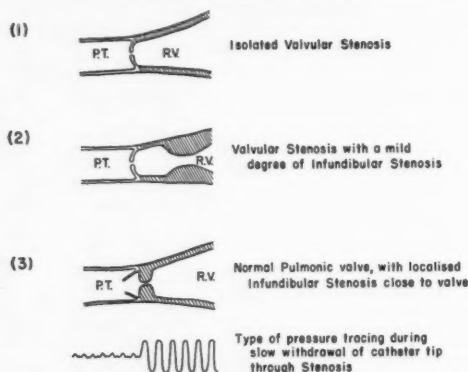
FIG. 8. Schematic representation of different types of pulmonic stenosis in which no intermediate pressure zone may be detected during slow withdrawal of the catheter tip from pulmonary artery to right ventricle. (1) Valvular stenosis; (2) valvular stenosis with a mild degree of infundibular stenosis; (3) normal pulmonic valve with localized infundibular stenosis close to valve.

If the degree of infundibular stenosis is not severe relative to the degree of stenosis existing at the valve, the pressure in the infundibular region may approach the right ventricular pressure in magnitude, and the presence of infundibular stenosis may not be recognized at catheterization (fig. 8).

SURGICAL CONSIDERATIONS

A. Identification of Site of Obstruction. The identification at the operating table of the type of obstruction present is unquestionably exceedingly important in the management of patients with pulmonic stenosis. The difficulty in recognizing accurately the nature of the obstruction is apparent from the disagreement that exists as to the incidence of valvular pulmonic stenosis in the tetralogy of Fallot[35-38];

however, it is also to be stressed that by careful examination of the outflow tract of the right ventricle and of the pulmonary artery, a good appraisal of the nature of the obstructing lesion may be made.

Two criteria exist, of which the more important, in our opinion, is the location of the thrill which is always present in these cases. If the thrill originates precisely at the orifice of the pulmonic valve, valvular pulmonic stenosis very probably exists. The diagnosis of valvular pulmonic stenosis is made nearly certain by noting the presence of a palpable, domelike, stiff pulmonic valve. These two criteria, the presence and location of the thrill and the palpable valve, are most important in our opinion.

It has been said that the sinuses of Valsalva are absent in valvular pulmonic stenosis. This may be true, but we have, in well-verified cases of valvular stenosis, seen a slightly bluish, thin-walled, localized area in the base of the pulmonary artery which is indistinguishable from the appearance of a sinus of Valsalva. In most cases of valvular pulmonic stenosis there is poststenotic dilatation of the pulmonary trunk. This may be present, however, in cases of infundibular stenosis and is, therefore, not a satisfactory criterion for distinguishing between these two types of obstruction.

The typical thrill may in some cases be felt to originate proximally to the junction of the outflow tract of the right ventricle and the pulmonary trunk. In such a case, it is highly probable that the obstruction is in the outflow tract of the right ventricle either alone or in combination with valvular pulmonic stenosis.

Unfortunately, the presence of the criteria enumerated for the diagnosis of valvular pulmonic stenosis does not exclude the possibility of an associated obstruction in the outflow tract of the right ventricle. It is our opinion that knowledge concerning this secondary obstruction is important, and it is for this reason that we believe that pressure recordings during the operation are of extreme value to the surgeon treating this type of malformation.[39] By such pressure tracings, one can identify the location of the primary obstruction and can identify a second obstruction if it is

present. By the same token, cases in which the more important site of the obstruction is in the outflow tract of the right ventricle may have an associated but less apparent valvular stenosis. In such instances, the gross criteria might lead one to the conclusion that only infundibular stenosis is present, whereas accurate pressure recordings during the operation would advise one of the associated presence of valvular stenosis.

In figure 9 is illustrated the type of tracing obtained during operation in a patient (case 10) with pulmonic stenosis and intact ventricular septum but with an atrial septal defect. This clinical diagnosis was confirmed at the time of cardiac catheterization, but no evidence of an infundibular stenosis was obtained. At operation, gross examination of the heart suggested the presence of infundibular stenosis, the typical dome of a stenotic pulmonic valve could not be felt, and the thrill began several centimeters proximal to the valve. With the more exact control of the catheter tip possible when the cardiac catheter was introduced directly into the right ventricle during operation, it was apparent from the pressure recording obtained during withdrawal of the catheter from the pulmonary trunk that the stenosis was a combined valvular and infundibular type.

In figure 10 are shown further recordings during operation in two patients (cases 8 and 9) with valvular and infundibular stenosis, one of whom had intact septa whereas the other had an atrial septal defect. In both, the diagnosis at operation, on the basis of examining the heart, was pulmonic valvular stenosis. In each of these patients prior to the incision and dilatation of the stenosed valve, the pressure recorded in the infundibular region approached closely that recorded in the low right ventricle. This finding indicated that the stenosis in the infundibular region was relatively mild compared with that existing at the valve. After incision and dilatation of the stenosed valve in each of these cases, a relative increase in the stenosis in the outflow tract was apparent as seen by the marked fall in pressure in the infundibular region while the right ventricular pressure was not reduced to the same degree.

B. Execution of a Complete Operation. In

this, as in all operative undertakings, it is important that the maximal improvement in the anatomic defect be attained by the operative procedure. This means that in cases of valvular pulmonic stenosis a vigorous attack must be made upon the stenotic pulmonic valve and that this attack must be continued until a very adequate opening is obtained. A complete opening may be obtained without the aid of pressure recordings during operation, providing the surgeon is diligent and persistent in his
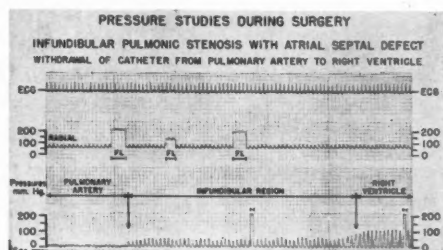
FIG. 9 (case 10). Pressures obtained at operation in a patient with combined valvular and infundibular stenosis with atrial septal defect. Upper tracing is the electrocardiogram; middle is radial arterial pressure; lower is pulmonary arterial and right ventricular pressure. At regions marked F1, the manometer-catheter systems were flushed with heparinized isotonic solution of sodium chloride in order to prevent clotting in the radial arterial needle or intracardiac catheter. The typical zone of intermediate pressure usually associated with combined valvular and infundibular stenosis was recorded during slow withdrawal of the tip of the catheter from pulmonary artery to right ventricle.

maneuvers; however, it has been of great assistance to us to have pressure recordings available during the operation.

Figure 11 illustrates continuous pressure recordings taken during operation in case 7 and shows the effect of successive incision and dilatations of the stenosed pulmonic valve. After the first incision and dilatation, which was thought to be adequate, a significant reduction in right ventricular pressure was achieved; however, since this was not of the degree desired, further dilatations of the valve were performed. After each dilatation, a further fall in pressure resulted and a more satisfactory end result was achieved than would have been the case had one been content with

the initial, apparently satisfactory, incision and dilatation of the valve.

C. *Representative Surgical Results.* Figures 12 and 13 show the type of operative results, as detected by pressure studies during operation, which can be achieved when relief of the stenosis has been almost complete. Figure 12 illustrates such findings in a child with valvular

stenosis (case 6) and atrial septal defect with an associated marked degree of peripheral arterial desaturation at rest. During the operation, recordings were made of both the right ventricular pressure and the peripheral arterial oxygen saturation. Three minutes after the incision of the stenosed valve and two minutes after its dilatation, the peripheral arterial
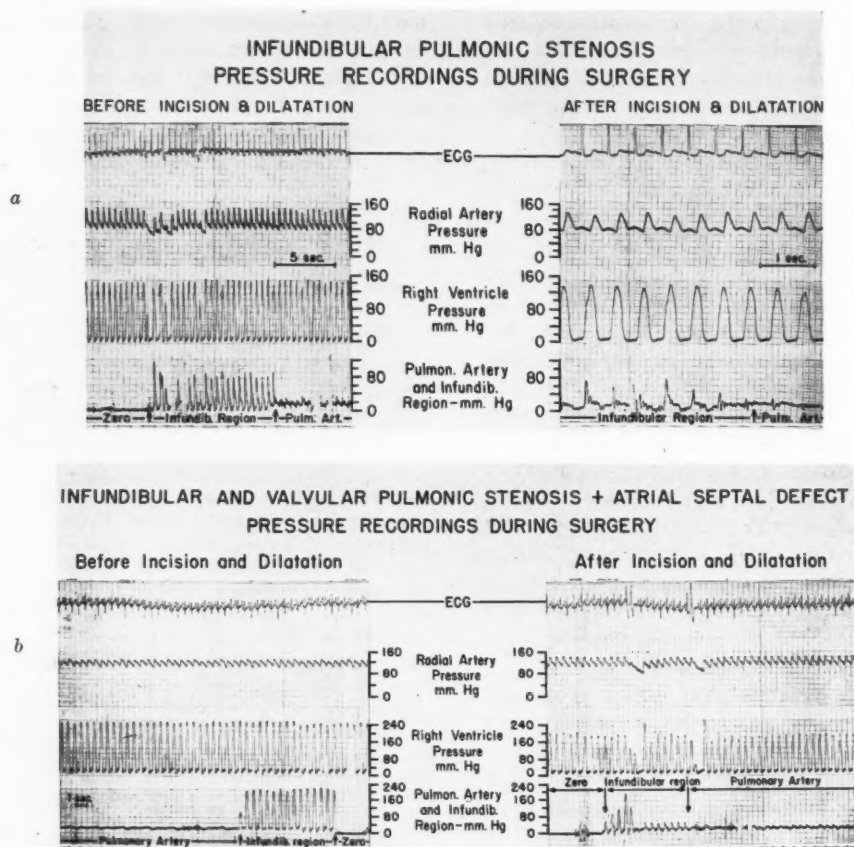
Fig. 10. Recordings obtained at operation in two patients with combined valvular and infundibular stenosis (*a*, case 8; *b*, case 9). Patient 9 had, in addition, an atrial septal defect. In each instance pressure in the cavity of the right ventricle was recorded by means of a catheter inserted through a needle placed into the lower part of the ventricle. Recordings in the outflow tract of the ventricle were made by means of a catheter inserted through the operative incision. Note that in each instance the systolic pressures in the infundibular region and right ventricle proper differ by about 40 mm. Hg before valvotomy. In each case, however, after incision and dilatation of the valve, the initial rise in pressure when the catheter tip is drawn through the valve is much less than before, indicating a marked degree of relief of the valvular stenosis. On the other hand, only a moderate decrease in the right ventricular pressure is evident in each, indicating that a gross degree of subvalvular stenosis still persists.

oxygen saturation had increased from 49 to 86 per cent. After operation, the right ventricular systolic pressure had decreased to 45 mm. Hg from its preoperative level of 150 mm. Hg. A very satisfactory relief of the pulmonic stenosis was achieved, as demonstrated by the pressure studies during operation and on examination of the operative result on the valve

tance of not more than 5 mm. proximal to the stenosed valve compared with the right ventricular pressure of 250 mm. Hg. Valvotomy and dilatations of the valve ring were followed by an immediate reduction of right ventricular systolic pressure from 250 mm. Hg to 70 mm. Hg. The intermediate zone of pressure, still measurable over the same very short distance
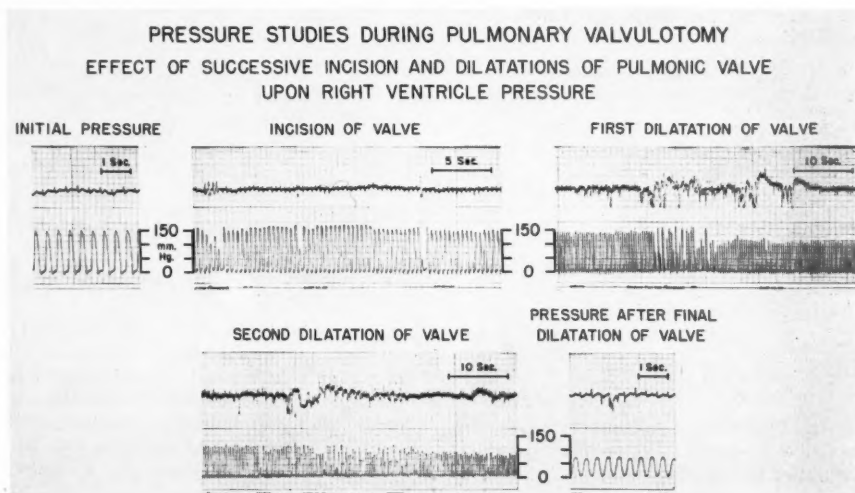
FIG. 11 (case 7). Effects of incision and successive dilatations of the pulmonic valve on right ventricular pressure in a patient who had pulmonic stenosis without septal defect. In each panel the upper tracing is the electrocardiogram (lead II) and the lower tracing is the right ventricular pressure. The first and last panels show, with a paper speed of 25 mm. per second, the initial and final right ventricular pressures, respectively. The second, third and fourth panels, recorded with paper speeds of 10, 5 and 5 mm. per second, respectively, are continuous tracings of right ventricular pressures during incision and successive dilatations of the valve. Note the irregularities and artefact in the electrocardiogram during dilatations of the valve and the abrupt decrease in right ventricular pressure after this procedure.

at necropsy. It was a bitter disappointment that this patient died of bilateral bronchopneumonia in the postoperative period.

Figure 13 shows a similar degree of surgical relief of the valvular stenosis (case 12). Preoperatively, it was felt that the stenosis resided mainly in the valve, although a relatively mild degree of subvalvular stenosis was suspected by reason of the recording of a slightly lower pressure in the immediate subvalvular region than was present in the right ventricle proper. This suspicion was confirmed at operation by the presence of an intermediate zone of pressure of 180 mm. Hg systolic for a dis-

of less than 5 mm., decreased from 180 to 50 mm. Hg while the pulmonary artery pressure increased from 18/10 to 25/15 mm. Hg.

It has been found that pressures recorded from the right ventricle during operation do not always correspond to those found at preoperative and postoperative cardiac catheterization. In many instances, probably due to increase in cardiac output during operation, the right ventricular systolic pressure recorded during operation was as much as 50 per cent greater than the resting value obtained at preoperative cardiac catheterization. Nevertheless, such pressure recordings during opera-

tion do give a good immediate index of the degree of relief of the stenosis which has been produced by the surgical procedure.

D. Problems in Surgical Management. In some instances, valvotomy may not give a good result in cases with coexisting valvular and infundibular obstruction. In such patients with combined valvular and infundibular types of stenosis, the magnitude of the abrupt pressure change at the pulmonic valve gives
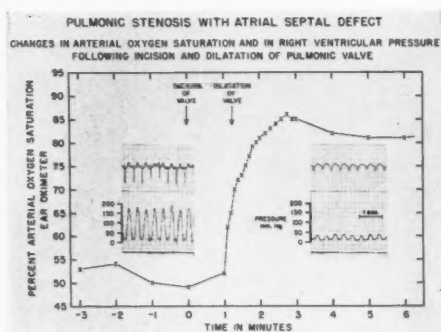
FIG. 12 (case 6). Effects of pulmonic valvotomy on right ventricular pressure and on peripheral arterial oxygen saturation in a child aged 3½ years who had valvular pulmonic stenosis and atrial septal defect. The oxygen saturation, obtained continuously by the absolute-reading ear oximeter,[44] is plotted on the ordinate against time (in minutes after incision of the valve) on the abscissa. Insets are electrocardiograms (lead I) and recordings of right ventricular pressures before and after incision and dilatation of the stenosed valve.

some measure of the degree of valvular stenosis, while the height of the right ventricular pressure gives a measure of the total stenosis.

In case 9, the right ventricular pressure recorded at operation, before valvotomy, was 254/15 while the pressure recorded immediately below the pulmonic valve was 220/15. After valvotomy, the right ventricular pressure was still very high, 200/15, but the height of the pressure recorded on withdrawal of the catheter through the valve was 50/15 mm. Hg. These findings suggested that an adequate valvotomy had been performed but that a marked degree of subvalvular stenosis still persisted. Because of this severe residual stenosis, the patient died 18 hours postoperatively. Examination of

his heart at necropsy, as described earlier, showed that an adequate valvotomy had been done but that a severe degree of subvalvular stenosis persisted, causing the maintained elevation of right ventricular pressure after valvotomy.
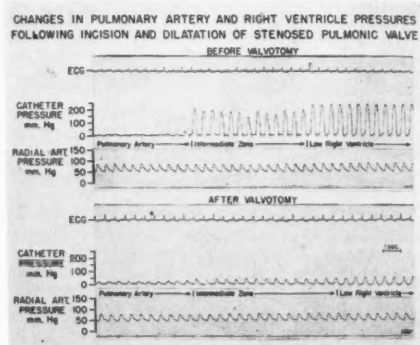
FIG. 13 (case 12). Changes in pulmonary arterial and right ventricular pressures following incision and dilatation of stenosed pulmonic valve. The electrocardiogram, radial arterial, and catheter pressure recorded during withdrawal of the catheter tip from the pulmonary artery to the right ventricle before incision and dilatation of the valve are shown in the upper panel; similar recordings after valvotomy are shown in the lower panel. As a result of valvotomy an appreciable decrease in right ventricular pressure from 248/8 to 72/5 mm. Hg was obtained, although some degree of valvular pulmonic stenosis remains. Note the intermediate zone of pressure which was demonstrated in the subvalvular region by the slow and controllable withdrawal of the catheter tip which was possible during operation. This intermediate pressure zone was detectable only over a distance of less than 5 mm., between the sites at which typical pulmonary arterial and right ventricular pressures, respectively, were recorded.

It is interesting to compare here the findings in case 10, in which there was also a combined valvular and infundibular stenosis. It was appreciated at operation that a considerable degree of subvalvular stenosis persisted following valvotomy, but it was felt that some benefit should follow the valvotomy. Cardiac catheterization six months postoperatively showed that a considerable fall in right ventricular pressure had taken place in spite of the persistence of the subvalvular stenosis after operation.

We have previously reported a case[40, case 3]

in which pulmonic valvotomy was done for what was assumed to be pure valvular pulmonic stenosis with intact ventricular septum and without an atrial septal defect. An unsatisfactory result was obtained and reoperation was effected. At the time of the second operation, it was recognized with the aid of pressure studies that the obstruction was now primarily in the outflow tract of the right ventricle. A type of plastic procedure was done upon this obstructing area with improvement as judged both by clinical evidence and by an increase

Studies of such a nature have been reported in occasional cases,[2-4, 41-43] and a fall in right ventricular pressure, a rise in pulmonary arterial pressure and a rise in arterial oxygen saturation have been noted after valvotomy. The most thorough and informative physiologic study was that recently published by Soulié and associates[43] concerned with nine cases. Right ventricular pressures fell rapidly in the immediate postoperative period and more slowly thereafter. The fall was more marked in individuals whose initial right ventricular

TABLE 3.—*Pressure Studies During Operation**

Case	Pressure, mm. Hg, before valvotomy				Pressure, mm. Hg, after incision and dilatation of valve			
	Pulmonary artery	Infundibular region	Right ventricle	Radial artery	Pulmonary artery	Infundibular region	Right ventricle	Radial artery
4	23/14		130/7	100/52	32/18		82/6	132/72
5	32/15	93/8	172/8		30/15		130/6	
6			165/15		32/20		42/15	
7			150/5	129/73	40/20		76/5	
8	30/17	90/5	150/5	140/83	23/15	50/5	130/5	130/80
9	34/27	220/15	254/15	130/110	28/19	50/15	200/15	165/120
10	14/8	50/5	125/5	100/70	13/8	25/5	110/5	100/70
11					25/15	45/5	140/5	
12	18/10	188/10	248/8	90/56	32/12	52/15	72/5	85/54

* Such studies were not done in cases 1, 2 and 3.

in cardiac output. Thus, on some occasions in patients with pulmonic stenosis and intact ventricular septum some procedure other than the routine valvotomy must be considered.

RESULTS OF OPERATION

There were two fatalities in this group of 12 cases. One was in the case outlined in an earlier paragraph in which the pulmonic stenosis was of such a type that we were unsuccessful in relieving it (case 9). This patient died without doubt because of unrelieved pulmonic stenosis. The second fatality occurred, as noted, because of bilateral bronchopneumonia (case 6).

All of the 10 patients in the group surviving the operation reported subjectively that they were "much improved." A similar result is reported by most authors in the literature. It is our belief, however, that the interpretation of such subjective results is fraught with many difficulties and that we must in this condition turn to more objective measurements.

pressure was greater than 150 mm. Hg than it was in those with initial pressures of 100 mm. Hg or less. These authors emphasized the fact that normal pressure values are not usually attained. They postulated that certain inherent factors in the congenital defect, particularly right ventricular hypertrophy with narrowing of the outflow tract, might continue to act as an obstruction to pulmonary blood flow postoperatively and explain the results observed.

The physiologic data obtained in our cases are presented in order that we may discuss the results of the operation in our group (tables 3, 4 and 5).

The ultimate benefit resulting from operation on patients with pulmonic stenosis can be judged best by postoperative cardiac catheterization. The immediate findings at operation are extremely valuable, but the results are, as noted previously, not strictly comparable with those observed at preoperative and post-

TABLE 4.—*Cardiac Catheterization Data*

Case	Diagnosis	Preoperative						
		Pressure, *mm. Hg*				Pulmonary blood flow, *L./min.*	Relative right ventricular outflow resistance*	Arterial saturation at rest, %
		Pulmonary artery	Infundibular region	Right ventricle	Radial artery			
1	Valvular stenosis and atrial septal defect	11/8		196/5	118/70	2.5	74.0	91
2	Valvular stenosis	18/10		55/5	113/65	3.9	9.5	96
3	Infundibular stenosis	15/10	12/2	120/2	130/77	5.6	18.8	97
4	Infundibular stenosis	20/12	20/2	145/2	138/76	5.4	23.0	96
5†	Combined valvular and infundibular stenosis			176/12		2.5		96
6	Valvular stenosis and atrial septal defect	20/15		140/10	80/50			65 (anesthetized)
7	Valvular stenosis	25/15		100/6	99/61	4.2	17.9	87 (anesthetized)
8‡	Combined valvular and infundibular stenosis	12/8		70/5		4.6	12.6	
9	Combined valvular and infundibular stenosis and atrial septal defect			196/12	156/113			72
10§	Combined valvular and infundibular stenosis and atrial septal defect	20/10		140/5	125/75	4.6	26.0	96
11	Combined valvular and infundibular stenosis and atrial septal defect		159/9	205/10				62 (anesthetized)
12	Combined valvular and infundibular stenosis and atrial septal defect	19/9	136/11	159/10	116/71	2.7	51.9	96

* Relative right ventricular outflow resistance $= \dfrac{\text{Systolic pressure gradient, mm. Hg}}{\text{Pulmonary blood flow, L./min.}}$.

† Reported in detail elsewhere.[40]

‡ Preoperative catheterization carried out at another institution, data made available.

§ Paroxysmal auricular tachycardia developed during preoperative and postoperative cardiac catherization.

operative cardiac catheterization in the unanesthetized patient.

There is no doubt that the best results can be achieved in patients with valvular stenosis as an isolated lesion. This can be understood by a study of the findings at operation in cases 6, 7 and 12 and from the preoperative and postoperative catheterization data in case 1.

A considerable degree of diminution in right ventricular pressure on occasions can be obtained after an adequate valvotomy in patients who have a combined valvular and infundibular stenosis. Further detailed studies over a prolonged period are necessary before one can determine whether subvalvular hypertrophy of the ventricular musculature diminishes following valvotomy in such patients. However,

it does appear as if the right ventricular pressure after valvotomy decreases progressively for a prolonged period as is seen in case 10.

The present series includes only two patients who had infundibular stenosis as an isolated lesion (cases 3 and 4). No dramatic diminution in right ventricular pressure followed dilatations of the infundibular stenosis but, in each instance, a moderate fall in right ventricular pressure followed operation. In case 3, a further fall in right ventricular pressure was found at cardiac catheterization 10 months after operation.

The studies on patient 11 are incomplete and evaluation of the effect of valvotomy must await postoperative cardiac catheterization.

Patient 2 was one of the first patients who

TABLE 5.—*Cardiac Catheterization Data*

Case	Diagnosis	Postoperative							
		Pressure, *mm. Hg*				Pulmonary blood flow, *L./min.*	Relative right ventricular outflow resistance*	Arterial saturation at rest, %	Postoperative period
		Pulmonary artery	Infundibular region	Right ventricle	Radial artery				
1	Valvular stenosis and atrial septal defect	16/12		65/8	90/60	3.6	13.6	93	3 weeks
2	Valvular stenosis	20/12		40/5	114/65	3.3	6.1	96	3 weeks
3	Infundibular stenosis	20/15		102/8	127/72	5.9	13.9	96	4 weeks
		19/8		80/3	130/72	5.1	12.0	98	10 months
4	Infundibular stenosis	25/15		100/5	123/65	5.4	13.9	94	2 weeks
5†	Combined valvular and infundibular stenosis								
6	Valvular stenosis and atrial septal defect								
7	Valvular stenosis								
8‡	Combined valvular and infundibular stenosis			56/4	145/65	7.1	6.2	94	6 weeks
9	Combined valvular and infundibular stenosis and atrial septal defect								
10§	Combined valvular and infundibular stenosis and atrial septal defect	20/12	50/8	65/8	110/71	4.0	11.3	96	5 months
11	Combined valvular and infundibular stenosis and atrial septal defect								
12	Combined valvular and infundibular stenosis and atrial septal defect								

* Relative right ventricular outflow resistance $= \dfrac{\text{Systolic pressure gradient, mm. Hg}}{\text{Pulmonary blood flow, L./min.}}$.

† Reported in detail elsewhere.[40]

‡ Preoperative catheterization carried out at another institution, data made available.

§ Paroxysmal auricular tachycardia developed during preoperative and postoperative cardiac catheterization.

underwent operation for pulmonic stenosis. Such a patient would not be operated on now but would be observed at intervals during adolescence. In general, it is now our practice not to operate on asymptomatic patients whose right ventricular systolic pressure is less than 70 to 75 mm. Hg.

For adequate interpretation of preoperative and postoperative pressure recordings at cardiac catheterization, details of flow should also be obtained so that the resistance to flow through the valve can be estimated. Comparative cardiac outputs are not always obtained under similar circumstances since the patient may be more apprehensive at the time of one cardiac catheterization than at another time of catheterization. Determination of right ventricular pressure and cardiac output following a period of exercise probably gives a better comparison of preoperative and postoperative values. As far as pulmonary artery and right ventricular pressures are concerned, pulmonary flow is the important variable, not systemic output. A "relative right ventricular outflow resistance" value has been included in tables 4 and 5. This value was obtained by dividing the systolic pressure gradient between right ventricle and pulmonary artery by the pulmonary artery flow (in liters per minute).

SUMMARY

1. The three types of anatomic obstruction to blood flow from the right ventricle to the pulmonary artery in patients with pulmonic stenosis and intact ventricular septum are discussed. Valvular stenosis in such cases may occur either alone or in combination with varying degrees of infundibular stenosis. Uncommonly, the latter may occur alone.

2. Physiologic data, gathered from patients with pulmonic stenosis and intact ventricular septum, are detailed. These again demonstrate that, in certain cases, valvular pulmonary stenosis is associated with some degree of infundibular stenosis.

3. Criteria for the differentiation at operation of valvular and infundibular pulmonic stenosis are enumerated.

4. The usefulness of accurate pressure tracings during operation is emphasized.

5. The accurate identification of the site or sites of obstruction to pulmonary blood flow is essential to proper surgical management. A correctly selected operation must be carried out in as complete a manner as possible.

6. Subjective and physiologic data are analyzed in the 12 cases reported.

ACKNOWLEDGMENT

SUMARIO ESPAÑOL

Obstrucción a la circulación pulmonar puede ocurrir en la válvula pulmonar, en el infundíbulo o en ambos. Cateterismo cardíaco ayuda a determinar el sitio de la obstrucción. El criterio para la diferenciación durante la operación entre estenosis infundibular o valvular se enumera y el uso de trazados exactos de la presión durante la operación se recalca. La identificación exacta del sitio o sitios de obstrucción a la circulación pulmonar es esencial para el manejo quirúrgico apropiado. Una operación correctamente seleccionada se debe conducir en la manera más complete posible.

REFERENCES

[1] Sellors, T. H.: Surgery of pulmonary stenosis: A case in which the pulmonary valve was successfully divided. Lancet 1: 988, 1948.

[2] Brock, R. C.: Pulmonary valvulotomy for the relief of congenital pulmonary stenosis: Report of three cases. Brit. M. J. 1: 1121, 1948.

[3] Blalock, A., and Kieffer, R. F., Jr.: Valvulotomy for the relief of congenital valvular pulmonic stenosis with intact ventricular septum: Report of nineteen operations by the Brock method. Ann. Surg. 132: 496, 1950.

[4] Potts, W. J., Gibson, S., Ricker, W. L., and Leininger, C. R.: Congenital pulmonary stenosis with intact ventricular septum. J. A. M. A. 144: 8, 1950.

[5] Adams, F. H., Veasy, L. G., Jorgens, J., Diehl, A., LaBree, J. W., Shapiro, M. J., and Dwan, P. F.: Congenital valvular pulmonary stenosis with or without an interatrial communication: Physiologic studies as diagnostic aids. J. Pediat. 38: 431, 1951.

[6] Allanby, K. D., and Campbell, M.: Congenital pulmonary stenosis with closed ventricular septum. Guy's Hosp. Rep. 98: 18, 1949.

[7] Auerbach, S. H., and Harber, H. T., Jr.: Congenital pulmonary stenosis with closed interventricular septum: Report of a case associated with patent foramen ovale and slight tricuspid stenosis. Am. Heart J. 34: 131, 1947.

[8] Bouilland: Quoted by Constanin, P.: Du retrissement de l'artere pulmonaire contracte apres la naissance. Bull. et mém. Soc. méd. hôp. Paris. 8: 45, 1871.

[9] Breda, R., and Fossati, F.: Stenosi congenita orifiziale isolata della polmonare in scompenso cronico. Folia cardiol. 10: 171, 1951.

[10] Brown, D. V., and McCollum, W. T.: Congenital pulmonary stenosis with intact interventricular septum. Am. J. Dis. Child. 80: 792, 1950.

[11] Carr, F. B., and Levi, H.: Pulmonary conus stenosis with closed fetal passages: Report of a case. Am. Heart J. 17: 243, 1939.

[12] Coelho, E., and De Oliveira, A.: Stenosis of the pulmonary infundibulum with intact ventricular septum: A case report with anatomic confirmation. Clín. contemp. 5: 57, 1951.

[13] Dammann, J. F., Jr., Gibson, S., and Potts, W. J.: Observations on 117 patients operated on for congenital pulmonary stenosis. Pediatrics 3: 575, 1949.

[14] Durand, M., and Metianu, C.: Présentation d'un cas de sténose congénitale pure de l'orifice pulmonaire avec vérification anatomique. Arch. mal. coeur 42: 1112, 1949.

[15] Engle, M. A., and Taussig, H. B.: Valvular pulmonic stenosis with intact ventricular septum and patent foramen ovale; report of illustrative cases and analysis of clinical syndrome. Circulation 2: 481, 1950.

[16] Greene, D. G., Baldwin, E. D., Baldwin, J. S., Himmelstein, A., Roh, C. E., and Cournand, A.: Pure congenital pulmonary stenosis and

idiopathic congenital dilatation of the pulmonary artery. Am. J. Med. **6:** 24, 1949.

[17] HILLMAN, R. W.: Congenital stenosis of the pulmonary valve in the absence of septal defects. Brooklyn Hosp. J. **4:** 26, 1946.

[18] HYMAN, A. L., LEVY, L., II, BAGNETTO, R., ORDWAY, N. K., AND HULL, E.: Isolated disease of the pulmonary valve and artery. Ann. Int. Med. **34:** 90, 1951.

[19] JOHNSON, R. P., AND JOHNSON, E. E.: Congenital pulmonic stenosis with open foramen ovale in infancy: Report of five proved cases. Am. Heart J. **44:** 344, 1952.

[20] KONWALER, B. E.: Cor triventriculare: Report of case. Am. Heart J. **27:** 259, 1944.

[21] LAVERAN, A.: Infarctus du coeur consécutif à la thrombose d'une des artères coronaires. Bull. et mém. Soc. med. hôp. Paris. **14:** 311, 1877.

[22] LEECH, C. B.: Congenital heart disease: Clinical analysis of seventy-five cases from the Johns Hopkins Hospital. J. Pediat. **7:** 802, 1935.

[23] LEITMANN, G.: Eine starke Stenose des Conus arteriosi d-ri als Folge einer fibrösen parietalen Endokarditis. Virchows Arch. path. Anat. **267:** 290, 1928.

[24] MARAIST, F., DALY, R., DRAPER, A., JR., HEIMBECKER, R., DAMMANN, F., JR., KIEFFER, R., JR., KING, J. T., FERENCZ, C., AND BING, R. J.: Physiological studies in congenital heart disease. X. The physiological findings in thirty-four patients with isolated pulmonary valvular stenosis. Bull. Johns Hopkins Hosp., **88:** 1, 1951.

[25] MÜLLER, H.: Die unkomplizierte angeborene Pulmonalstenose. Schweiz. med. Wchnschr. **55:** 619, 1925.

[26] NYSSENS, A., AND VAN BOGAERT, A.: Observation anatomoclinique et radiologique d'un cas de sténose pulmonaire orificielle isolée. Arch. mal. coeur **42:** 75, 1949.

[27] ORDWAY, N. K., LEVY, L., II, HYMAN, A. L., AND BAGNETTO, R. L.: Pulmonary stenosis with patent foramen ovale. Am. Heart J. **40:** 271, 1950.

[28] SELZER, A., CARNES, W. H., NOBLE, C. A., JR., HIGGINS, W. H., JR., AND HOLMES, R. O.: The syndrome of pulmonary stenosis with patent foramen ovale. Am. J. Med. **6:** 3, 1949.

[29] SUSSMAN, M. L., SCHWARTZ, B. M., BRAHMS, S. A., AND KING, F. H.: The diagnosis of patent foramen ovale in cases of congenital pulmonary stenosis, including one case of levocardia. Arizona Med. **7:** 21, 1950.

[30] THIELEN, E. O., AND JANUARY, L. E.: Stenosis of the pulmonary conus without associated defects: A case report. J. Iowa M. Soc. **41:** 88, 1951.

[31] WALSHAM, H.: Stenosis of the pulmonary orifice

of the heart. (Card. specimen.) Tr. Path. Soc. London, **47:** 25, 1896.

[32] WEINBERG, T.: Pulmonic valve stenosis in an adult unassociated with interventricular or interauricular septal defects, and with a closed foramen ovale. J. Tech. Methods **32:** 22, 1951.

[33] WHITE, P. D., HURST, J. M., AND FENNELL, R. H.: Survival to age of 75 years with congenital pulmonary stenosis and patent foramen ovale. Circulation **2:** 558, 1950.

[34] WOOD, P.: Congenital pulmonary stenosis: With left ventricular enlargement associated with atrial septal defect. Brit. Heart J. **4:** 11, 1942.

[35] BROCK, R. C., AND CAMPBELL, M.: Infundibular resection or dilatation for infundibular stenosis. Brit. Heart J. **12:** 403, 1950.

[36] BURKE, E. C., KIRKLIN, J. W., AND EDWARDS, J. E.: Sites of obstruction to pulmonary blood flow in the tetralogy of Fallot: An anatomic study. Proc. Staff Meet., Mayo Clin. **26:** 498, 1951.

[37] GLOVER, R. P., BAILEY, C. P., O'NEILL, T. J. E., DOWNING, D. F., AND WELLS, C. R. E.: The direct intracardiac relief of pulmonary stenosis in the tetralogy of Fallot. J. Thoracic Surg. **23:** 14, 1952.

[38] JOHNS, T. N. P., WILLIAMS, G. R., AND BLALOCK, A.: The anatomy of pulmonary stenosis and atresia with comments on surgical therapy. Surgery **33:** 161, 1953.

[39] CONNOLLY, D. C., LEV, R., KIRKLIN, J. W., AND WOOD, E. H.: The problem of isolated valvular versus infundibular pulmonic stenosis with particular reference to cardiac catheterization data and records obtained at the time of operation. Proc. Staff Meet., Mayo Clin. **28:** 65, 1953.

[40] KIRKLIN, J. W., OPENSHAW, C. R., AND TOMPKINS, R. G.: Surgical treatment of infundibular stenosis with intact ventricular septum: Report of a case. Ann. Surg. **137:** 228, 1953.

[41] GALLIGAN, J. J., ADAMS, F. H., AND JORGENS, J.: Congenital pulmonary stenosis without cyanosis. J. Pediat. **41:** 562, 1952.

[42] SCHUMAKER, H. B., JR., AND LURIE, P. R.: Pulmonary valvulotomy: Description of a new operative approach with comments about diagnostic characteristics of pulmonic valvular stenosis. J. Thoracic Surg. **25:** 173, 1953.

[43] SOULIÉ, P., JOLY, F., CARLOTTI, J., SICOT, J. R., AND VOCI, G.: Étude physiopathologique postopératoire de la triologie de Fallot. (Étude de neuf cas après valvulotomie pulmonaire.) Arch. mal. coeur **45:** 385, 1952.

[44] WOOD, E. H., AND GERACI, J. E.: Photoelectric determination of arterial oxygen saturation in man. J. Lab. & Clin. Med. **34:** 387, 1949.

Orthostatic Factors in Pulsus Alternans

By Ben Friedman, M.D., William M. Daily, M.D., and Roy S. Sheffield, M.D.

Ventricular alternans was present in three cardiac patients only in the erect or semierect position and disappeared with recumbency. The phenomenon which was regularly reproduced in the standing posture was prevented or minimized by exercise, digitalis, infusions of blood and norepinephrine and by application of external vascular support. Ventricular alternation in the supine patient was noted only after phlebotomy, or venous pooling combined with Valsalva maneuvers. The observations suggest that in the mechanism of this type of pulsus alternans there is an important peripheral hemodynamic factor which exerts its effect by changes in diastolic length of an injured ventricular muscle.

IN THE past two years we have observed three patients with heart disease in whom pulsus alternans was strikingly related to posture. Ventricular alternans was present only in the erect or semierect position and disappeared with recumbency. The phenomenon could be reproduced at will, thus affording an opportunity to study some of the mechanisms concerned in its production.

The three subjects were considered to have varying degrees of organic heart disease. One person (J. W.) had hypertension with previous congestive heart failure, another (R. H.) had had congestive failure due probably to arteriosclerotic coronary artery disease, and the third individual had myocardial disease of uncertain etiology with an abnormal electrocardiogram and radiologic evidence of cardiac enlargement.

Case Reports

Case 1. J. W., a 55 year old Negro veteran had complained of various aches and pains in the back and extremities dating back to 1920. In 1935 he had an episode of pneumonia in the left lung; since then pains in the left anterior chest and subscapular region were added to his other skeletal pains. The pains were not specially related to effort, but he had not worked since 1935. He was then observed in numerous hospitals and treated for osteoarthritis of the spine. Dyspnea on exertion was present for 15 years. In February 1949, hypertension was noted for the first time at a level of 190/130. Persistent hypertension had been observed during the ensuing two years. In February 1950, he had increasing dyspnea and was given digitalis. In October 1950 he had stopped taking digitalis and developed paroxysmal dyspnea and mild pulmonary edema. In March 1951

he was admitted with principal complaints of headaches, dyspnea, back ache and paresthesias. The significant findings at this time were blood pressure of 200/150, hypertensive retinopathy with marked narrowing of the retinal vessels, arteriovenous nicking and occasional exudate, and moderate cardiac enlargement. There was a grade II systolic blowing murmur at the base. The venous pressure was 13 cm. H_2O and the arm-to-tongue circulation time was 20 seconds. Pulsus alternans was present in the erect position, the difference in systolic pressure between the strong and weak beat amounting to as much as 30 mm. Hg. The electrocardiogram showed evidence of left ventricular hypertrophy. There was slight albuminuria and the maximum urine concentration was 1.020. The maximum urea clearance was 48 per cent and the phenolsulfonphthalein excretion was 5 per cent in 15 minutes. The excretory urogram showed an essentially normal configuration. The reaction to benzodioxane injection was normal. The clinical impression was hypertensive cardiovascular disease and arteriolar nephrosclerosis.

Case 2. R. H., a 44 year old Negro man, was well until April 1949 when he first noted swelling of the ankles and dyspnea. The swelling progressed rapidly to the legs and abdomen. The dyspnea grew worse but was never prominent. During the ensuing two years he was observed in Veterans' Hospitals on three occasions. Each time he was found to have frank congestive heart failure with marked peripheral edema, pleural effusion, hepatic enlargement, elevated venous pressure and signs of pulmonary congestion, diffuse cardiac enlargement, gallop rhythm and markedly prolonged arm-to-tongue circulation time (35 to 55 seconds). On each occasion treatment with low salt diet, digitalis and diuretics effected prompt symptomatic improvement with loss of about 25 pounds of edema fluid and diminution in the size of the heart.

The etiology for the heart disease was not apparent. There had been no history of rheumatic fever or clinical signs of valvular disease. There were no evidences of syphilis by history, physical signs or laboratory tests. A blood pressure of 140/110 was

present on one occasion during a period of severe failure. At other times the blood pressure readings were within the normal range (120/90, 120/92, 98 66). There was no history of previous hypertension or renal disease and no definite retinal vascular abnormalities. Although he was a moderate beer drinker, the dietary intake was considered to be adequate. There was no anemia. The determinations of the basal metabolic rates, when he was free of dyspnea, ranged between minus 9 and minus 19 per cent, and the serum cholesterol values were slightly elevated (260 to 380 mg. per 100 cc.), but there were no other findings to suggest hypothyroidism. Although he had not complained of chest pain, the electrocardiographic changes suggested the probability of coronary disease (absent R wave in V_1 to V_4, flat or inverted T waves in leads I, II, II, V_5 and V_6, and reversal of polarity of T wave in chest leads after exercise).

He was readmitted in February 1951. The break in compensation, like the one preceding, was precipitated by discontinuing digitalis and a low salt diet. In addition to the signs of congestive failure it was noted that he had definite pulsus alternans which was detected in the semierect or sitting posture, but was not apparent in the reclining position. A diffuse apical impulse was felt in the anterior axillary line in the left sixth intercostal space. The heart rate was 100, the rhythm normal and no murmurs were heard. Blood pressure was 120/90. Orthostatic pulsus alternans was still present in September 1953.

Case 3. E. B., a 48 year old Negro man, was admitted in July 1950, complaining of periumbilical and epigastric pain, nausea and vomiting of four days duration. A similar episode had occurred for the first time in April 1943, and required treatment in a military hospital. Since then he had had attacks of burning epigastric pain of a pattern resembling peptic ulcer. A transient syncopal spell occurred in 1945 and was accompanied by dark stools. There was no additional history to suggest hemorrhage. In May 1948, he was treated at this hospital for uncomplicated duodenal ulcer. No clinical evidence of cardiac disease was noted at that time. Blood pressure was 128/90. An electrocardiogram was not taken. Fluoroscopic examination showed the heart and aorta to be normal. The blood serologic tests for syphilis were either negative or doubtful. There were no corroborative evidences of syphilis either by history or physical signs. There was no history of angina pectoris or of previous hypertension.

On admission in July 1950, he appeared well-nourished and developed and in no acute distress. There was slight, diffuse, midabdominal tenderness. There were varicose veins below the knee in both legs. The heart was not definitely enlarged. The heart rate was 110 per minute. In the sitting position every other pulse beat was weak and at times almost imperceptible. On assuming the reclining position the alternating pulse disappeared, and the rate declined

slightly. The blood pressure reading, which initially was 150/106, declined shortly afterward to a level of 100/76. On subsequent examinations the blood pressure has usually been within normal range with occasional diastolic readings above 100 mm. Hg.

The pertinent laboratory data were as follows: Barium meal showed a clover-leaf deformity in the duodenum but no definite crater. The hemoglobin was 16.3 Gm., and repeated stool examinations were negative for occult blood. The serum chloride and bicarbonate were respectively 103 and 21 mEq. per liter. Fluoroscopic and x-ray examination of the chest revealed definite increase in size of heart over that noted two years previously. The electrocardiogram in the recumbent position was abnormal, showing diphasic T waves in leads I and II, deep Q_3 and late deep inversion of T waves in V_4, V_5 and V_6.

It was suspected at first that we were dealing with an acute myocardial infarction, and the patient was kept in bed for two weeks. The temperature, white blood count and sedimentation rate remained normal. The electrocardiogram did not show the progressive changes characteristic of an infarction. With management of the ulcer, the symptoms subsided. The phenomenon of pulsus alternans occurred only in the erect posture and was observed repeatedly at different intervals during the next 12 months.

The electrocardiographic changes and the increase in size of the heart persisted during the period of follow-up. The etiology of the heart disease was not clear. He had no symptoms of failing myocardial reserve and was not given digitalis.

INFLUENCE OF VARIOUS PROCEDURES UPON ALTERNATION

Effect of Body Position

The subjects reclined comfortably on a table which could be tilted to any desired angle. Records were made of the carotid or carotojugular pulse, electrocardiogram and heart sounds. Blood pressures in the arm were determined by means of a sphygmomanometer in the usual manner. When pulsus alternans was present, independent systolic readings could usually be registered for strong and weak beats. In some instances the electrokymogram and the femoral arterial pressure tracings were recorded.

In two subjects (R. H. and J. W., fig. 1) pulsus alternans was absent in the recumbent position and appeared first a few minutes after the body was tilted to an angle of 15 or 30 degrees from the horizontal. At a 60 degree angle the ventricular alternans was much more

pronounced, the systolic level of the weak beat being about 20 mm. Hg below that of the strong beat of the couple. In the third individual (E. B., fig. 1) alternation of the beat could not be regularly induced except at an angle of at least 75 degrees, and then only after standing for five or six minutes. The longer he

Pulsus alternans was recorded in the erect posture at pulse rates varying from 70 to 110 per minute, but usually in the range of 90 to 110. The heart rates in all three subjects were faster in the vertical posture when pulsus alternans was present than in the horizontal position. The differences usually amounted to
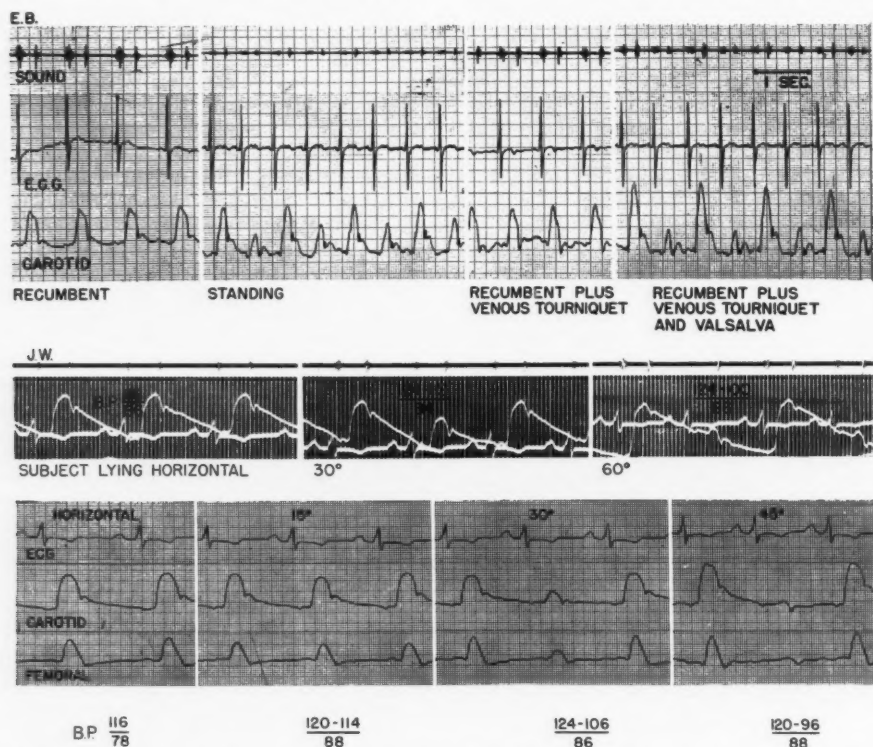
Fig. 1. Posture and pulsus alternans in three patients. Time interval between heavy vertical lines = 0.2 second in upper and middle tracing (E. B. & J. W.) and 0.1 second in lower tracing (R. H.)

remained erect the more prominent it became. At times the weak beat produced an impulse too faint to be detected at the wrist. In all 3 persons tilting back into the horizontal position resulted in a prompt disappearance of the alternation.

These observations were repeated on numerous occasions during the ensuing year. Pulsus alternans was regularly present in the erect posture, varying only in degree and in the length of time required for the subject to remain standing before it became apparent.

10 to 30 beats per minute. Tachycardia of ectopic origin was never observed. The vertical posture was accompanied by minor alterations in blood pressure usually in the direction of a rise in the diastolic level and either no change or a slight rise in the systolic level. Postural hypotension was not present.

The electrocardiograph registered impulses of sinus origin and of identical configuration. Electrical alternans was not noted. Isolated beats of ectopic origin occurred sporadically and were then followed either by transient

accentuation of an existing ventricular alternation or by the induction of alternation for a period of six or eight beats.

Electrokymographic tracings obtained during periods of pulsus alternans in the erect posture showed concordant alternation in amplitude of ventricular contraction (fig. 5). This phenomenon was usually best recorded from aortic and left ventricular borders with the patient in the anteroposterior or left lateral roentgen position. An alternating pattern was not observed in tracings of the pulmonary arterial and auricular movements. As compared with the strong beat of the couple, the weak beat was characterized at its inception by a lesser level of diastolic filling and during contraction by an altered slope of systolic ejection and less complete emptying of the ventricle resulting in a fuller ventricular chamber (larger residual volume) at the end of systole.

Effect of External Hydrostatic Pressure

The effects of external hydrostatic pressure upon orthostatic alternation were observed while the patients were standing in a swimming pool filled with tepid water. Observations were begun as the subjects stood at the pool's edge, when alternation was marked. The subjects then descended by steps into the water, stopping for recordings on each step. In this manner the degree of external hydrostatic pressure was increased with the level of immersion from ankles to midchest.

It may be seen (fig. 2 A1–A5 B1–B5) that, as the water level rises above the hips, there is a gradual increase in the strength of the weak beat. Immersion to the midchest level abolished the alternation in one subject and nearly abolished it in the other for as long as the subjects stood in the water to this depth. Upon emergence from the water the tendency to alternation in strength of beat reappeared or became accentuated.

Effect of Abdominal and Leg Binders

To two patients in the supine position with the legs elevated above the head elastic bandages were applied firmly from the feet to the

inguinal ligaments. Abdominal binders also were placed snugly in position. The subjects were then placed upright.

In each instance (fig. 2a) binding of the legs and abdomen prevented the development of pulsus alternans, which had unfailingly ap-
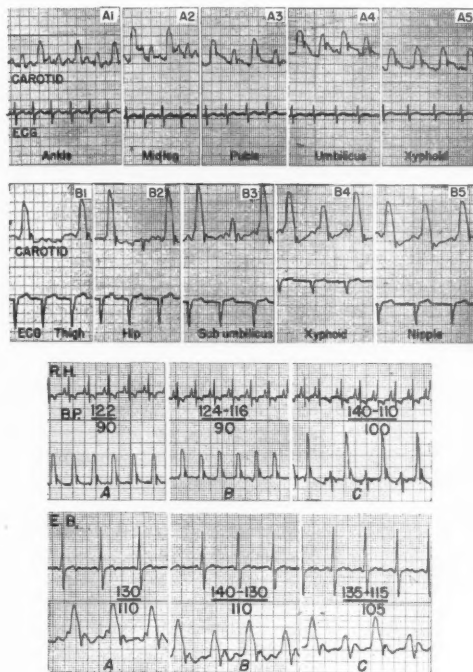
Fig. 2. Effect of external vascular support on pulsus alternans.

Upper two tracings: patients standing in water at increasing levels of hydrostatic pressure. Patient E. B. = A1–A5. Patient R. H. = B1–B5.

Lower two tracings: Patients standing with elastic bandages. (*A*) Abdominal and leg binders in place. (*B*) Abdominal binders removed, leg binders in place. (*C*) Abdominal and leg binders removed.

peared previously in the erect position. With abdominal binders removed but leg binders in place a slight degree of alternation resulted (fig. 2b). Within two minutes after all the binders had been released (fig. 2c) alternation became pronounced in both subjects, the pulse rate remaining unchanged or accelerating slightly.

Effect of Exercise

Pulsus alternans was induced by placing the subject in the erect posture on the tilt table. He was then permitted to exercise in place for a period of 30 to 90 seconds by lifting the legs.

Figure 3 represents the changes observed in typical experiments. In subject E. B. exercise resulted in a prompt disappearance of ventricular alternation despite an acceleration in

beat became stronger after 300 cc. of blood had been infused, and at the end of the infusion period the pulse rate was 95 per minute and blood pressure 116/80. Pulsus alternans had entirely disappeared (fig. 4). During the ensuing 30 minutes, although the patient remained in the erect position, no alternation appeared except for four beats immediately following a premature ventricular systole.
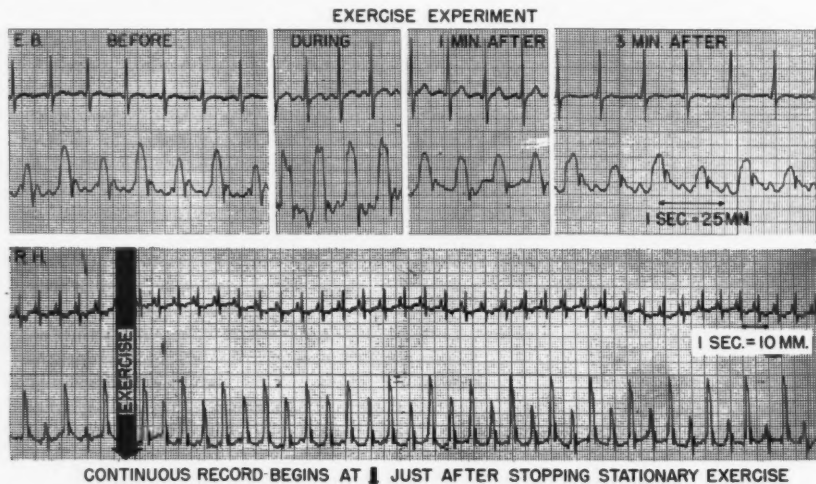
FIG. 3. Effect of exercise on pulsus alternans. *Upper record* made before exercise, during and one and three minutes after completion of stationary exercise in erect posture. *Lower recording* stopped at arrow 60 seconds for exercise, and restarted immediately after completion of exercise.

heart rate of 20 beats per minute. In subject R. H. the strength of the weak beat was augmented after exercise but did not attain the full volume of the strong beat of the couple. Cessation of exercise was followed by rapid decline in amplitude of the weak beats prior to any appreciable change in heart rate.

Effect of Infusion of Blood and of Phlebotomy

In subject E. B. pulsus alternans was elicited with the patient on the tilt table at an angle of 78 degrees. The pulse rate fluctuated between 100 and 110 per minute, and the blood pressure was 110/75. Alternation was pronounced. The difference between strong and weak beat was more than 30 mm. Hg, in fact, no systolic pressure was detected for the weak beat. Five hundred cc. of matched whole blood were infused over a period of 20 minutes. The weak

On a different occasion, in the same individual an attempt was made to induce alternation of the pulse by means of phlebotomy while the patient was in the recumbent position. After 950 cc. of blood were withdrawn, the pulse rate increased from 87 to 107 per minute, but pulsus alternans was not present except for a transient period following immediately upon a premature beat. Prolonged alternation independent of premature beats appeared when the tilt table was elevated to an angle of 20 degrees from the horizontal, a position in which spontaneous ventricular alternation had never been present in this subject (fig. 1). While in this position alternation was stopped temporarily by light exercise, and completely when half of the previously removed blood volume had been reinfused.

At another time in this patient we did such

ceed in inducing temporary alernation in the completely recumbent posture. This was accomplished by means of venous occlusion tourniquets applied to all four extremities and the performance of a Valsalva maneuver at the same time (fig. 1).

centimeter, was infused intravenously for two minutes at a rate of 20 to 40 drops per minute. The pulse rate declined to 62 per minute simultaneously with a rise in blood pressure. When the blood pressure reached a level of 160/125 two minutes after beginning the infu-
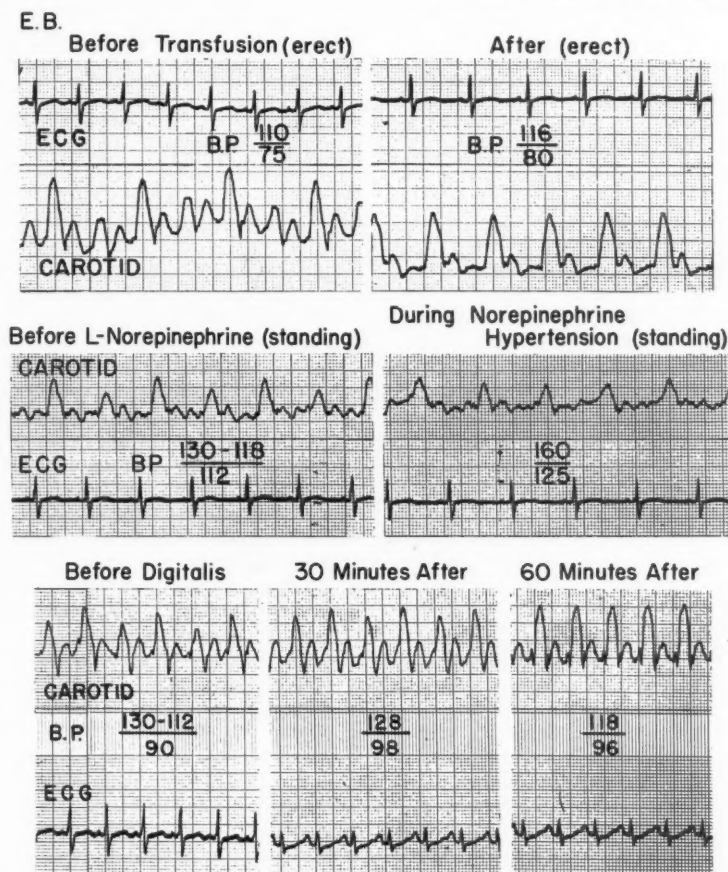
FIG. 4. Effects of digitalis, infusion of norepinephrine and blood on pulsus alternans. Time interval between solid vertical lines = 0.2 second.

Effect of Norepinephrine and Digitalis

Subject E. B. was resting on a tilt table in the erect posture at an angle of 80 degrees. The pulse rate was 108 and ventricular alternans was definitely present, the difference between strong and weak beats being about 12 mm. Hg $\left(\text{blood pressure } \frac{130 \text{ and } 118}{113}\right)$. Norepnephrine in saline, 4 micrograms per cubic

sion, pulsus alternans disappeared (fig. 4). Alternation reappeared within four minutes after stopping the infusion as the blood pressure returned to the preinfusion level. After a short rest period this experiment was repeated with identical results.

The effect of digitalization on orthostatic alternation was observed in subject E. B. who had never before been given digitalis in any

form. On this occasion, after having been standing for one hour, he had a pulse rate of 145 per minute, with marked pulsus alternans. In this position he was given lantoside C, 1.6 mg., intravenously. During the ensuing hour, although he remained standing, ventricular alternation tended to disappear for short intervals. One hour after the injection, by which time digitalis effects were present in the electrocardiogram, alternation disappeared for a 25-minute period. This reduction of orthostatic alternation was effected after digitalization, despite a concurrent increase in heart rate to 150 (fig. 4).

DISCUSSION

True ventricular alternation must be distinguished from pseudoalternans which may closely simulate it. The latter is observed often in bigeminy associated with periodically recurring premature ectopic beats or with sino-auricular or auriculoventricular conduction defects. It has been described in association with rapid breathing when the respiratory rate is half the pulse rate.[1] Dyspnea was not present in the three patients here described at the time of these observations, and indeed most of the records were made with the patients holding the breath in the midrespiratory position. The electrocardiograms recorded during periods of pulsus alternans showed impulses of sinus origin and of similar cycle length and configuration for strong and weak beats with no variation in duration of P-R or Q-T intervals or QRS complex. In some records careful measurement disclosed a minute but periodic alternation in cycle length varying between 0.005 to 0.04 second but generally about 0.01 second in duration, the weak beat of the couple appearing closer in time to the antecedent than to the following strong beat. We have noted such slight periodic variations in cycle length in individuals with normal heart rates and true pulsus alternans unrelated to body position. A similar observation was made by Wenckebach.[2]

It is well known that a benign type of pulsus alternans may occur with disturbances of rhythm in an otherwise normal heart. Mechanical alternation of temporary duration has been observed following premature beats and

for prolonged periods in association with marked tachycardia.[3,4] Premature beats of ventricular origin were recorded in two of our three patients on several occasions. They were invariably followed in succession by a compensatory pause, a strong post-extrasystolic beat and either alternation of the pulse for six or eight beats or else an exaggeration of an already existing ventricular alternans for three or four couples. Ectopic beats never induced pulsus alternans of prolonged type. The latter was recorded in both subjects over periods of two or three hours without the appearance of a single ectopic beat.

The question arises whether the appearance of ventricular alternation in our cases is related solely to changes in heart rate. We do not believe this proposition to be valid for the following reasons: (1) The heart rates at which pulsus alternans appeared were frequently in the range of 80 to 90 per minute but varied widely in the same individual. (2) The differences in heart rate between the horizontal (nonalternating) posture and the vertical (alternating) position were small, being 10 to 30 beats per minute. (3) Following digitalis (fig. 4) and exercise (fig. 3) there was a lessening of the tendency to ventricular alternans in the face of no change or a slight increase in heart rate. While acceleration in heart rate undoubtedly exerts an important influence in the mechanism of pulsus alternans, we do not believe that the magnitude of the change here encountered constitutes the major factor in the induction of alternation in the erect position.

The patients described here have in common the existence of organic heart disease and pulsus alternans which is manifest in the erect or semierect posture and absent in the recumbent position. The most obvious mechanism by which postural changes might influence the mechanical performance of the heart is by actions on the venous return, cardiac output and ventricular diastolic volume. The observations on these subjects and the postulated physiologic actions may be summarized as in table 1.

Those procedures which induced or amplified pulsus alternans curtail venous return and hence decrease ventricular diastolic volume.

Procedures which increase ventricular diastolic volume either by augmenting venous return or by increasing peripheral resistance tended to inhibit or abolish ventricular alternans. The favorable effect of digitalis in one case may be attributed to its action in improving efficiency of myocardial contraction so that increased work performance and presumably better emptying is accomplished with a shorter initial fiber length.[8] Windle[9] noted similar results of digitalis in cardiac patients.

TABLE 1.—*Summary of Observations and Postulated Physiologic Actions*

Procedure	Physiologic Effect	Effect on Pulsus Alternans
Erect posture	Diminish venous[5, 6] return and cardiac output	Induce or intensify
Recumbent posture Exercise Hydrostatic pressure Elastic bandages Increase blood volume	Increase venous return and cardiac output	Abolish or diminish
Nor-epinephrine	Increase peripheral resistance[7]	Abolish or diminish
Digitalis	Improved myocardial efficiency[8]	Abolish or diminish

The nearest approximation to the ventricular volume curve in our patients is the record of the left ventricular border movement as seen in the electrokymogram. The positional changes and artefactual movements that complicate the interpretations are admitted, but these objections are minimal in comparing consecutive beats in the same heart. In all of our kymographic tracings the strong beats begin at higher levels of diastolic volume than do the intervening weak beats and empty the heart more completely (fig. 5).

It is proposed that in these patients with diseased heart muscle the total contracting power is not sufficient to empty the ventricle normally under usual conditions of diastolic

fiber length. A greater stretch, hence a more generous end-diastolic volume, is required to produce a strong beat. This end-diastolic volume is the sum of the residual volume just after systole plus the venous inflow during diastole. Under conditions of diminished diastolic filling, pulsus alternans comes about as follows: The weak beat fails to empty the ventricle, leaving a large residual volume; to this large residual volume is added the venous

Electrokymogram in Pulsus Alternans
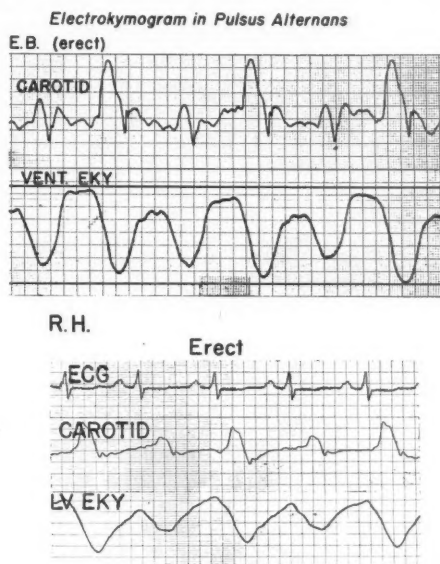
FIG. 5. Left ventricular electrokymogram in pulsus alternans. Time interval between solid vertical lines = 0.1 second.

inflow, producing a large end-diastolic volume; because the end-diastolic volume is then adequate, a strong beat follows and empties the ventricle more completely; the remaining small residual volume plus the venous inflow leads to too small an end-diastolic volume for an optimum contraction, and a weak beat ensues.

The relative contributions of myocardial versus hemodynamic factors to the genesis of pulsus alternans has been a subject of discussion for more than 50 years. Wenckebach[2] was the first to champion the concept that changes in ventricular filling and peripheral resistance may cause transient as well as sustained pulsus alternans quite apart from myogenic disturb-

ances. Wiggers[3] supported this view with respect to the experimentally induced ventricular alternation which follows a prolonged diastolic pause. This type of alternation is temporary and occurs only in a rapidly beating heart. While all of the phenomena could be explained purely on the basis of hemodynamic alterations in his experimental preparation, Wiggers carefully emphasized the possibility of the importance of myocardial factors in other types of pulsus alternans.

Many investigators[3, 10, 11] have emphasized the prime importance of variations in initial tension and volume in the mechanism of ventricular alternation. The point at issue has been whether the changes in volume and tension arise from primary alterations in vigor of muscle contraction or whether the latter are secondary to variations in inflow and resistance.

Greene[12] demonstrated that pulsus alternans that follows experimentally induced coronary insufficiency is due to periodic defections in contractile power of varying fractions of ischemic muscle in alternate beats. He believed that dynamic changes are not dominantly concerned in the mechanism of ventricular alternation since the degree of stretch in the weak beat was as great or greater than in the strong beat. His records show that the differences in degrees of stretch as registered by the myograph occur not at the end of diastolic filling but just prior to systolic ejection; during the period of isometric contraction. Lengthening of the muscle fiber of the localized area of injury at this point in the cycle reflects combined effects due to changes in diastolic volume plus changes in shape secondary to loss of contractile power. The greater fiber length in the weak beat may be interpreted as representing a greater degree of passive ballooning rather than increased stretch at the end of diastole. This evidence does not exclude the possibility of a significant hemodynamic factor.

Wiggers, a life-long investigator of this disturbance, recently summarized his views as follows: "It appears highly probable that ventricular alternation always involves the defection of some fractionate contractions during the small beat. However, changes in the intensity of alternation do not necessarily signify quantal variations in the deletion of fractionate contractions. They can be induced by secondary dynamic factors which alter diastolic distention and initial tension."[13]

The observations in patients with orthostatic alternation are in accord with this concept. Some procedures, such as exercise, augmented blood volume and acute hypertension, that abolished alternation in the standing subject can hardly have exerted their effect by improving myocardial contractability. Nor is it easy to visualize changes in intrinsic muscle contractile function arising as a result of immersing the body in water or of elevating the upper half 30 degrees.

We have not observed orthostatic alternation of the pulse in persons with normal hearts. Each of our three patients had evidence of diseased myocardium. In two it was severe enough to lead to congestive heart failure. Orthostatic hypotension was not present. One individual (E. B.) had prominent venous varicosities in the legs. He frequently displayed a rise in heart rate of 20 to 30 beats per minute on changing from the horizontal to the vertical position. External compression of the legs alone, whether applied by bandages or water, was not effective in entirely preventing the alternating phenomenon in this instance. The other two subjects had no detectable evidence of vasomotor instability or venous pooling. We have observed three additional patients with heart disease and classic pulsus alternans which was present in the recumbent position but which was intensified on assuming the erect posture. It is, therefore, suggested that our three cases are not instances of an unusual vasomotor disturbance but rather accentuated forms of a phenomenon which may be common to all types of pulsus alternans.

We are not aware of any previous report in which the orthostatic posture is associated with pulsus alternans either to bring out a latent alternation or to exaggerate one which already exists.

It is evident that pulsus alternans may be completely overlooked in the recumbent subject. The patient who has been standing for

several minutes affords the optimum conditions for the detection of ventricular alternation.

SUMMARY

1. Three patients with organic myocardial disease demonstrated the phenomenon of pulsus alternans which was strikingly related to body position.

2. Measures which tended to induce or exaggerate alternation were erect posture, phlebotomy, venous pooling plus tourniquets and, for short periods, premature beats.

3. Procedures which tended to prevent or abolish ventricular alternations were recumbency, exercise, digitalis, norepinephrine, transfusion of blood and application of external vascular support.

4. The observations support the view that there are two factors concerned in this type of alternation: (a) weakened or injured heart muscle which does not contribute sufficient contractile strength to empty the ventricle efficiently except under conditions of increased stretch; and (b) a precipitating extracardiac hemodynamic factor which exerts its effect by changes in ventricular inflow and peripheral resistance.

5. The detection of pulsus alternans may be facilitated if the patient is examined in the sitting or standing position.

SUMARIO ESPAÑOL

Alternans ventriculares se encontraron presentes en tres pacientes cardíacos en la posición vertical o semivertical pero desaparecieron con la reclinación. El fenómeno que fué reproducido con regularidad en la posición parada fué obviado o reducido al mímino mediante el ejercicio, digitalis, infusiones de sangre y norepinefrina y mediante la aplicación de soportes vasculares externos. Alternación ventricular en el paciente supino se observó solamente luego de flebotomía o estancamiento venoso combinado con las maniobras de Valsalva. Las observaciones sugieren que en el mecanismo de este tipo de pulso alternans hay un factor hemodinámico periférico importante que ejerce su afecto por medio de cambios en el largo diastólico del músculo ventricular averiado.

REFERENCES

[1] SWINGLE, P. F.: Training of the heart by systematically regulating the respiration. Am. J. Physiol. **74:** 82, 1925.

[2] WENCKEBACH, K. F.: Die unregelmässige Herztätigkeit und ihre Klinisch Bedertung. Leipzig und Berlin, Verlag von W. Engelmann, 1914, P. 209.

[3] LEWIS, T.: The Mechanism and Graphic Registration of the Heart Beat. London, Shaw and Sons, 1925.

[4] WIGGERS, C. J.: The Cause of Temporary Ventricular Alternation Following a Long Diastolic Pause. A. S. Warthin Anniversary Volume. Ann Arbor, George Wahr Pub., 1927.

[5] McMICHAEL, J., AND SHARPEY-SCHAFER, E. P.: Cardiac output in man by direct Fick method. Effect of posture, venous pressure change, atropine and adrenaline. Brit. Heart J. **6:** 33, 1944.

[6] SCHNEIDER, E. C., AND CRAMPTON, C. B.: The effect of posture on the minute volume of the heart. Am. J. Physiol. **110:** 14, 1935.

[7] GOLDENBERG, M., PINES, K. L., BALDWIN, E. DE F., GREENE, D. G., AND ROH, E. E.: The hemodynamic response of man to nor-epinephrine and epinephrine and its relation to the problem of hypertension. Am. J. Med. **5:** 792, 1948.

[8] STARLING, E. H., AND VISSCHER, M. D.: The regulation of the energy output of the heart. J. Physiol. **62:** 243, 1922.

[9] WINDLE, J. D.: Clinical observation on the effect of digitalis in heart disease with pulsus alternans. Quart. J. Med. **10:** 274, 1917.

[10] KAHN, R. H.: Zum problem des Herzalternans. Arch ges Physiol. **181:** 65, 1920.

[11] KATZ, L. N., AND FEIL, H. S.: Clinical observations on the dynamics of ventricular systole. IV. Pulsus alternans. Am. J. M. Sc. **194:** 601, 1937.

[12] GREENE, H. D.: The nature of ventricular alternans resulting from reduced coronary blood flow. Am. J. Physiol. **114:** 407, 1936.

[13] WIGGERS, C. J.: Circulatory Dynamics. Modern Medical Monographs, No. 4. Grune & Stratton, New York, 1952. P. 78.

Effects of Papaverine upon Ectopic Ventricular Tachycardia Produced by Myocardial Infarction

By A. Sidney Harris, Ph.D., Antonio Estandía, M.D., Abdo Bisteni, M.D., and Herbert T. Smith, M.D.

Papaverine hydrochloride exhibited some ectopic impulse suppressor effect which was brief in duration and could not be maintained. Additional doses led to toxic reactions including *increased* ectopic activity. No consistent correlation was found between changes in blood pressure and decreases or increases in ectopic frequency. Vasodilator potency of drugs apparently bears no intimate relation to ectopic impulse suppressor effect.

LIGATION of the anterior descending artery of the dog's heart by a standard technic[1] produces ectopic ventricular tachycardia after a delay of four and one-half to eight hours. Untreated, the tachycardia continues two to four days and there may be some ectopic beats on the fifth day. This persistent ectopic ventricular tachycardia that develops with myocardial infarction is difficult to suppress with drugs, and the standardization of the method has provided an exacting test preparation.[2, 3, 4]

It has been shown by other investigators that papaverine raises the fibrillation threshold (intimately related to threshold for premature systoles) of the dog's ventricles to brief direct current stimuli[5] and reduces the excitability of the dog's auricles to faradic stimuli.[6] The excised papillary muscle of the cat exhibited increased excitability to induction shocks when treated with papaverine in concentrations below 4.5×10^{-2} mmol., and excitability was reduced by higher concentrations. Automaticity was induced by the higher concentrations, generally within the range that diminished excitability to shocks.[7] Papaverine has been reported effective in abolishing auricular and ventricular premature beats in patients for brief periods,[8] but evidence of its action in ventricular tachycardia is meager or lacking.

In the following series of experiments the effects of papaverine hydrochloride upon ventricular tachycardia resulting from myocardial infarction in dogs was tested.

Procedures

Under pentobarbital sodium anesthesia and with aseptic surgical precautions the dog's heart is exposed via an incision in the fourth intercostal space on the left side. The anterior descending artery is dissected free for a distance of about 2 mm. at the level of the free edge of the left auricular appendage. A doubled ligature is then passed under the artery and cut, making two ligatures. A partial occlusion is produced by tying one ligature snugly but not tightly around the artery together with a 20 gage hypodermic needle. The second ligature is tied tightly around the artery after an interval of 30 minutes. By this two-stage occlusion technic, losses by early ventricular fibrillation following occlusion are avoided. The chest is closed and the animal is given postoperative care.

Electrocardiograms are made prior to operation and at frequent intervals afterward, especially just before and during tests. On the morning of the first postoperative day, 16 to 20 hours after occlusion, a number of control electrocardiograms are made and testing is begun. At this time almost all animals have a rapid ectopic ventricular tachycardia which is persistent and exhibits only minor changes in frequency from hour to hour. The frequency varies in different animals, from about 150 to 260 per minute. The great majority exhibit frequencies between 170 and 250, but occasional frequencies as high as 300 and lower than 150 are recorded.

The administration of papaverine was by the intravenous route in all tests. Each dose was diluted to 10 cc. with Locke's Solution and injected at a uniform rate during a period of two or five minutes.

RESULTS

The effects of papaverine were tested in six dogs, three with *low frequency* ventricular tachycardias (160 per minute and less) and three with *high frequency* tachycardias (180 to 250)). In experiments with certain other drugs, low frequency ectopic activity has been more easily controlled than the higher frequency tachycardias.[2, 4]

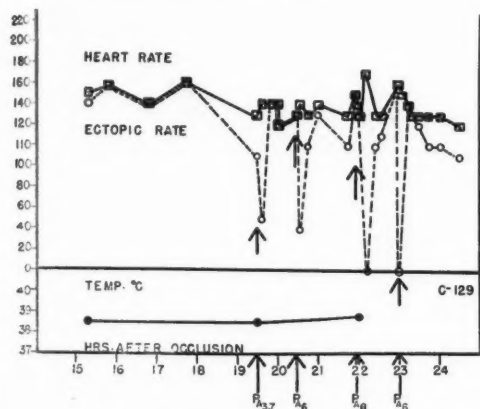Figure 1 is a chart showing ectopic impulse suppressor effect, brief in duration, 15 to 30

FIG. 1. Effects of papaverine upon low-frequency ventricular tachycardia.

minutes at most, following each of four doses of papaverine in one of the animals with a low frequency ventricular tachycardia, 140 to 160 per minute before treatment. The doses were varied from 3.7 mg. per kilogram in the first injection to 8 mg. per kilogram in the largest one. After the last dose, the ectopic rate tended to level off at about 100 to 110 per minute. No additional doses were given because of the severe vomiting produced by the last two.

In the other two animals in the low-frequency tachycardia group there were brief periods of markedly reduced frequency of the tachycardia or brief restoration of sinus rhythm. The effect could not be sustained, however, even with the administration of additional doses. After a total dosage of about 20 mg. per kilogram additional injections usually increased ectopic activity. In one of these animals the administration of papaverine during

periods of sinus rhythm *produced* ventricular tachycardia, and in certain trials in other animals the ectopic rate was temporarily increased immediately after the injection and diminished a few minutes later. This sequence of changes occurred twice in the same animal after earlier injections had produced only diminutions in frequency. The increase in ectopic activity or the induction of it by papaverine is regarded as one of the toxic manifestations of the drug.

Electrocardiograph and blood pressure records were made continuously during certain injections given to a dog in which papaverine produced ventricular tachycardia. The record made during one of the injections (fig. 2) shows that the paroxysm of tachycardia began just before, or simultaneously with, the beginning of the decline of blood pressure. It did not follow the fall in pressure. Therefore, the tachycardia was not secondary to this reduction. It continued unchanged during the period of increased hypotension. The arterial pressure was already depressed in this animal by the cumulative effects of previous doses of papaverine.

The administration of papaverine to animals with high frequency ventricular tachycardias (180 to 250) also exhibited a small degree of ectopic impulse suppressor effect for brief periods after some doses, and an increase of ectopic activity after other doses. Figure 3 is a reproduction of electrocardiograms from an animal with an ectopic frequency of 240 per minute just prior to the first 10 mg. per kilogram dose of papaverine. The ectopic frequencies in four control records made during the last hour before the beginning of the test ranged between 200 and 250. The tracing in record B shows (in measurement from a longer section) an ectopic rate of 160. This was the lowest ectopic rate achieved during the experiment. It followed the third 10 mg. per kilogram dose. The ectopic frequency in record C made 15 minutes after the fourth dose, is 220. Record D, made immediately after completion of the fifth dose, shows the ventricular fibrillation that developed, apparently as a result of increase in ectopic activity during the fifth injection. This was the only death by ven-

tricular fibrillation that resulted from papaverine administration. The other two dogs with high frequency tachycardias died in cardiac arrest after repeated doses of papaverine, 10

tion occurred after 50 mg. per kilogram total in two hours.

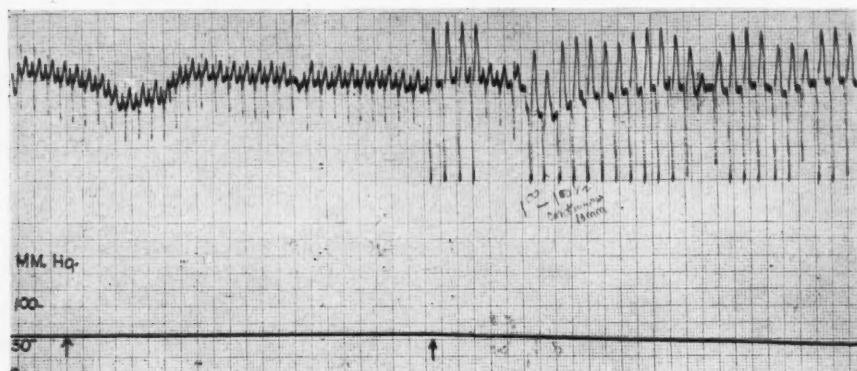*Blood Pressure.* The administration of papaverine, 10 mg. per kilogram, produced a decline

FIG. 2. Continuous record during injection of papaverine showing production of paroxysm of ventricular tachycardia. First arrow designates beginning of injection; second arrow points to beginning of the ventricular tachycardia. Duration of injection extends beyond end of figure. Speed of recording 10 mm. per second.
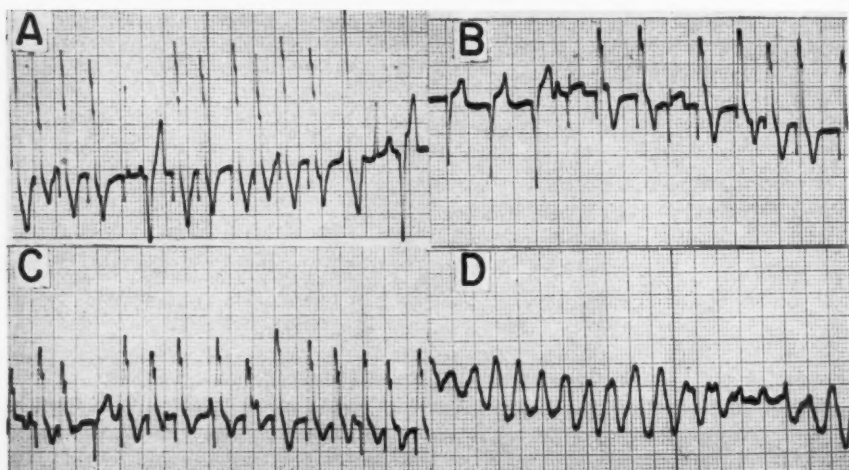
FIG. 3. Effects of papaverine in animal with high frequency tachycardia.

mg. per kilogram, had failed to interrupt the tachycardia even for brief periods.

One death by cardiac arrest occurred after doses totaling 50 mg. per kilogram in two an one-half hours and the other after a total dosage of 60 mg. per kilogram in one and one-half hours. The death by ventricular fibrilla-

in blood pressure in all trials. Each dose was diluted with Locke's solution to 10 cc. and injected slowly during a period of two minutes or five minutes. The reductions in pressure during and following the five-minute injections ranged from 15 to 35 mm. Hg. The reductions produced by the two-minute injections ranged

from 25 to 40 mm. The control pressure usually was not fully regained between doses. Therefore, there was an irregular decline throughout the duration of the tests. There was no consistent correlation between changes in blood pressure and changes in ectopic frequency. Following some injections there was diminution in ectopic rate and in blood pressure. Following certain other injections, there was increased ectopic rate during the diminution in blood pressure.

DISCUSSION

Papaverine produced some significant reductions in ectopic frequency in animals with low and moderate frequency ventricular tachycardia and relatively smaller reductions in high frequency tachycardia. These reductions were brief in duration.

The severity of toxic reactions, including increases in ectopic frequency, that resulted from repeated and increased doses given in attempts to obtain lasting suppression of ectopic impulses, indicate that papaverine probably would have little or no practical value for the treatment of ventricular tachycardia accompanying myocardial infarction, and that it could be dangerous if administered in large quantities to patients with high frequency ventricular tachycardia.

The observation, made in the animal in which ventricular tachycardia was produced by papaverine, that the tachycardia began before the blood pressure declined is of interest in regard to the mechanism by which papaverine excites the discharge of ectopic impulses. This observation rules out the possibility that the tachycardia was initiated by a reflex action evoked by hypotension. Other conceivable mechanisms are (1) that papaverine directly excites the myocardium (probably in the frontier of the infarct) to discharge impulses or (2) that it excites the sympathetic nervous system, and possibly the adrenal medulla in some manner not depending upon hypotensive reflex mechanisms. Greiner and Garb[7] have shown that papaverine can induce automaticity in excised papillary muscle of the cat's heart; therefore the sympathoadrenal system need

not necessarily be involved, though it might contribute to the total effect.

Some experiments have recently been made with dioxylene phosphate (Paveril phosphate), which is closely related to papaverine chemically and has greater vasodilator potency, relative to acute toxicity.[9, 10] Dioxylene phosphate failed to exhibit a useful degree of ectopic impulse suppressor action as did nitroglycerin also (both unpublished). It is clear that ectopic suppressor action is not to be anticipated on a basis of demonstrated vasodilator action even though the best known ectopic suppressor compounds (quinidine, procaine amide, magnesium) have vasodilator properties.

SUMMARY

Some ectopic impulse suppressor effect was observed following intravenous injections of papaverine hydrochloride to dogs with ventricular tachycardia resulting from myocardial infarction. The effect was brief in duration, and could not be maintained by additional doses.

After a total dosage of about 20 mg. per kilogram in one to two hours, additional doses usually *increased* ectopic activity. Ventricular tachycardia was induced in one animal that had sinus rhythm just prior to the injection of papaverine, and ventricular fibrillation followed shortly after an injection in another. Papaverine has both ectopic impulse suppressor effects and ectopic impulse inducing effects. Neither effect appears to be correlated with the direction of change of blood pressure. Possible mechanisms by which ectopic activity may be produced by papaverine are discussed.

From the study of papaverine and other potent vasodilators, namely dioxylene phosphate and nitroglycerin, it is concluded that useful ectopic impulse suppressor action cannot be anticipated on a basis of vasodilator effect.

SUMARIO ESPAÑOL

Clorhidrato de papaverina mostró tener un efecto supresivo para impulsos ectópicos que fué de duración breve y no se pudo mantener. Dosis adicionales produjeron reacciones tóxicas

incluyendo actividad ectópica aumentada. No se pudo encontrar correlación alguna entre los cambios en presión arterial y decrementos o incrementos en frecuencia ectópica. El poder vasodilatador de la droga aparentemente no tiene relacción alguna al afecto supresivo para impulsos ectópicos.

REFERENCES

[1] HARRIS, A. S.: Delayed development of ventricular ectopic rhythms following experimental coronary occlusion. Circulation 1: 1318, 1950.

[2] —, ESTANDÍA, A., FORD, T. J., JR., AND TILLOTSON, R. F.: Quinidine lactate and gluconate in the suppression of ectopic ventricular tachycardias associated with myocardial infarction. Control of toxicity by morphine. Circulation 4: 522, 1951.

[3] —, —, —, SMITH, H. T., OLSEN, R. W., AND TILLOTSON, R. F.: The effects of intravenous procaine and procaine amide (Pronestyl) upon ectopic ventricular tachycardia accompanying acute myocardial infarction. Circulation 4: 551, 1951.

[4] —, —, SMITH, H. T., OLSEN, R. W., FORD, T. J., JR., AND TILLOTSON, R. F.: Magnesium sulfate and chloride in suppression of ectopic ventricular tachycardia accompanying acute myocardial infarction. Am. J. Physiol. 172: 251, 1953.

[5] WÉGRIA, R., AND NICKERSON, N. D.: The effect of papaverine, epinephrin and quinidine on the fibrillation threshold of the mammalian ventricles. J. Pharmacol. & Exper. Therap. 75: 50, 1942.

[6] ELEK, S. R., AND KATZ, L. N.: The action of papaverine on the heart of the dog. J. Pharmacol. & Exper. Therap. 74: 335, 1942.

[7] GREINER, T. H., AND GARB, S.: The influence of drugs on the irritability and automaticity of heart muscle. J. Pharmacol. & Exper. Therap. 93: 215, 1950.

[8] ELEK, S. R., AND KATZ, L. N.: Clinical uses of papaverine in heart disease. J. A. M. A. 120: 434, 1942.

[9] HENDERSON, F. G., SHIPLEY, R. E., AND CHEN, K. K.: Pharmacologic studies of 6,7-dimethoxy-7-(4'-ethoxy-3'-methoxybenzyl)-3-methyl isoquinoline. J. Am. Pharmacol. A. 40: 207, 1951.

[10] SCOTT, R. C., SEIWERT, V. J., FOWLER, N. O., JR., AND McGUIRE, J.: Studies on the use of dioxyline phosphate in the treatment of angina pectoris. Circulation 6: 125, 1952.

Evaluation of Routine Serial Fluoroscopic Examinations of the Heart in the Postero-anterior and Oblique Views at Specific Degrees of Rotation

With Special Reference to the Angle of Clearance of the Left Ventricle

By May G. Wilson, M.D., Nathan Epstein, M.D., Helen N. Helper, M D., and Katharine Hain, M.D.

An evaluation of 2973 serial fluoroscopic examinations at specific degrees of rotation for 500 subjects 2 to 21 years of age, made by 35 different observers with an average of five examiners per patient, is presented. In the postero-anterior view, 1 per cent showed convexity of the pulmonary segment. In the right anterior oblique position 1 per cent showed retrodisplacement of the esophagus. The angle of clearance of the left ventricle in the left anterior oblique position was less than 55 degrees in 90 per cent of the fluoroscopic examinations. In addition, 1393 routine serial fluoroscopic examinations of 100 patients with inactive rheumatic heart disease, 4 to 48 years of age, were analyzed. There was a total of 49 observers, an average of 8 per patient. The angle of clearance of the left ventricle ranged between 55 and 70 degrees. There was left auricular enlargement in 98 patients. It is concluded that fluoroscopic examination at specific degrees of rotation is a reliable procedure for detecting cardiac chamber abnormality, and should be included as part of the routine examination.

THE CLINICAL importance of fluoroscopic examination of the heart in the frontal and oblique views to detect abnormality of the individual chambers is now well established.[1, 2, 3] It is not as well recognized that serial fluoroscopic examinations at specific degrees of rotation afford opportunities for detection of slight degrees of chamber enlargement. This is particularly important for the early diagnosis of active carditis.

In 1934 an investigation was made of roentgenologic criteria for cardiac chamber enlargement.[4] This included cardiothoracic index, cardiac surface area and radioscopic examination in oblique views at specific degrees of rotation. In 504 children it was found that

radioscopic examination in the oblique views differentiated normal from abnormal hearts with the greatest degree of frequency in comparison with the frontal view. The left ventricle cleared at less than 55 degrees in 97 per cent of 119 normal children. It was concluded that the fluoroscopic procedure described was a simple, reasonably accurate method for detecting cardiac chamber abnormality. Kuttner and Reyersbach[5] used a comparable technic on 101 children selected from an orphanage who did not present evidence of heart disease on physical examination. Seventy-seven per cent of these children had an angle of clearance of the left ventricle of less than 55 degrees.

This report concerns an evaluation of the reliability of routine serial fluoroscopic examination for the detection of cardiac chamber abnormality with special reference to the angle of clearance of the left ventricle. The fluoroscopic technic followed differed in no way from that previously described.[6]

The recorded routine fluoroscopic examina-

tions of 500 children from 2 to 21 years of age who were under continuous medical supervision during the past 15 years as part of a family study were analyzed. The children were fluoroscoped at least annually and during any febrile illness as part of the physical examination. The 2973 fluoroscopic examinations were made by 35 different observers of varied experience. There was an average of five different examiners per child. Fluoroscopic examinations of children presenting evidence on
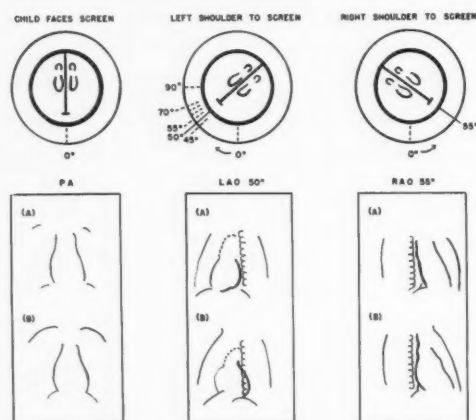

Fig. 1. Fluoroscopic examination of the cardiac silhouette at specific degrees of rotation. (A) A normal child. (B) A child with rheumatic heart disease; note encroachment of the left ventricle on the body of the vertebra at 50 degrees rotation in the left anterior oblique, and retrodisplacement of the barium-filled esophagus in the right anterior oblique position.

physical examination of organic heart disease, kyphosis, scoliosis, funnel or pigeon breast, were excluded from this analysis. Fluoroscopic examinations of 26 children who developed rheumatic fever while under observation were excluded at the onset of symptoms.

For comparison, 1393 routine serial fluoroscopic examinations of 100 rheumatic patients 4 to 48 years of age, under medical supervision in the Cardiac Clinic during the past 18 years, were also analyzed. These examinations were made by 49 different observers with an average of eight different examiners per patient.

OBSERVATIONS

Table 1 shows the distribution of pertinent findings in 2973 routine serial fluoroscopic examinations for 500 patients 2 to 21 years of age. It will be noted that in 1 per cent of the fluoroscopic examinations there was sporadic convexity of the pulmonary segment and in another 1 per cent retrodisplacement of the barium filled esophagus was noted. In 10 per cent, the angle of clearance of the left ventricle was 55 degrees or more.

In table 2, the variations observed in the angle of clearance of the left ventricle in the left anterior oblique position are presented.

TABLE 1.—*2973 Serial Fluoroscopic Examinations of the Heart in 500 Normal Subjects, 2 to 21 Years of Age—Abnormalities*

Posterior-Anterior 2+ convexity of pulmonary segment		Right Anterior Oblique 1+ retrodisplacement of barium filled esophagus		Left Anterior Oblique Angle of clearance of the left ventricle, 55 degrees or more	
Pts.	Fluoros.	Pts.	Fluoros.	Pts.	Fluoros.
25 (5%)	36 (1%)	20 (4%)	31 (1%)	98 (20%)	306 (10%)

TABLE 2.—*Angle of Clearance of Left Ventricle in 2973 Serial Fluoroscopic Examinations in 500 Normal Subjects 2 to 21 Years of Age*

	Degree of Rotation			
	Between 45–50°	50°	Between 50–55°	55° or more
No. of fluoroscopic examinations	299	1824	544	306
% of fluoroscopic examinations	(10%)	(61%)	(18%)	(10%)

In 10 per cent of the fluoroscopic examinations, the angle of clearance was less than 50 degrees; in about two-thirds it was 50 degrees, and in about one-fifth it was more than 50 degrees but less than 55 degrees. It will be seen that in 90 per cent of the fluoroscopic examinations (80 per cent of the children) the angle of clearance was less than 55 degrees, confirming the observations of the previous investigations.[6]

The angle of clearance was less than 50 degrees in vertically placed hearts and slightly more than 50 degrees in transverse hearts, particularly in obese children with high diaphragms. Following periods of rapid growth the angle of clearance was observed to decrease slightly. Sporadic variations in the angle of

clearance were observed three times as often in the age group of 6 to 13 years than before or after this age period.

Of the 98 patients (20 per cent) who showed angles of clearance of 55 degrees or more occasionally, this occurred in 35 patients once, in 18 twice and in 45 patients three or more times. In patients with persistent angles of clearance between 50 and 55 degrees, slight lordosis was frequently observed. In 53 patients observed to have angles of clearance of 55 degrees one or more times, it was recorded that there was poor posture or poor cooperation.

Progressive increases in the angle of clearance of the left ventricle and retrodisplacement of the esophagus were noted in 26 patients who developed rheumatic fever while under observation. It is important to note that patients experiencing febrile illnesses did not have any detectable change in the cardiac silhouette in the postero-anterior or oblique views.

In 100 patients with inactive rheumatic heart disease, aged 4 to 48 years, observed for 2 to 18 years in the Cardiac Clinic, 12 had aortic and mitral insufficiency with mitral stenosis, 28 had mitral insufficiency and stenosis, 50 had mitral insufficiency and 10 patients had uncharacteristic systolic murmurs with cardiac chamber enlargement. In 1393 serial fluoroscopic examinations of these patients the angle of clearance in this group ranged from 55 to 70 degrees. There was left auricular enlargement in 98 patients. In 90 per cent of the fluoroscopic examinations the angle of clearance of the left ventricle did not vary in the absence of a recurrent attack of rheumatic fever. In 10 per cent of the fluoroscopic examinations there were variations of 5 degrees or more. This occurred most frequently in patients with angles of clearance of 60 or 65 degrees. It is significant that although cardiac chamber enlargement persisted unchanged, characteristic murmurs of valvular deformity regressed in 28 patients during the period of observation and became uncharacteristic in 46.

COMMENT

In recent years fluoroscopic examination has become part of the routine examination in office and clinic practice. In differentiating the normal from the abnormal heart, the normal variations in cardiac silhouette due to body build must be considered. The reliability of the angle of clearance of the left ventricle as an index of left ventricular enlargement depends on the care exercised to avoid errors. It is essential that the child stand erect, arms at the side, and be cautioned not to move. The clearance of the left ventricle from the bodies of the vertebra should be observed during normal respiration. The low incidence of variations in the angle of clearance of the left ventricle in the routine serial fluoroscopic examinations at specific degrees of rotation by observers of varied experience is worthy of note. The possibility that the examiners were influenced by previous fluoroscopic findings was considered. It was found, however, that variations occurred as frequently when performed by the same as by different examiners.

The observations presented confirm the reliability of the fluoroscopic criteria established in the previous investigation. Of particular interest is the finding that the normal angle of clearance was less than 55 degrees in 90 per cent of the serial fluoroscopic examinations.

The normal range in the angle of clearance, that is, between 45 and 55 degrees, emphasizes the importance of including fluoroscopy as part of the initial examination. This is especially important in children of rheumatic families in whom slight changes in the cardiac silhouette, within the normal range, would make possible an early diagnosis of active carditis. However, an angle of clearance of 55 degrees or more would appear to be presumptive evidence of left ventricular enlargement.

The fluoroscopic evidence of cardiac chamber enlargement is of special importance in patients with inactive rheumatic heart disease in whom auscultatory signs of valvular deformity regressed or became uncharacteristic. It is obvious that residual cardiac damage in rheumatic fever cannot be excluded on physical examination alone.

SUMMARY AND CONCLUSIONS

An evaluation of 2973 routine serial fluoroscopic examinations in the posterior-anterior

and oblique views at specific degrees of rotation is presented for 500 normal subjects. These patients, 2 to 21 years of age, were under medical supervision during a 15-year period of observation as part of a family study. Examinations were made by 35 different observers of varying experience, with an average of five observers per patient.

In the posterior-anterior view, 1 per cent of the fluoroscopic examinations revealed convexity of the pulmonary segment.

There was retrodisplacement of the barium filled esophagus in 1 per cent of the examinations in the right anterior oblique position.

In the left anterior oblique view the angle of clearance of the left ventricle was less than 50 degrees in 10 per cent, 50 degrees in 61 per cent, between 50 and 55 degrees in 18 per cent and 55 degrees or more in 10 per cent of the fluoroscopic examinations. In 90 per cent of the serial fluoroscopic examinations the angle of clearance was between 45 and 55 degrees.

These observations on normal subjects were compared with 1393 routine serial fluoroscopic examinations of 100 patients, 4 to 48 years of age, under medical supervision in the Cardiac Clinic with inactive rheumatic heart disease for the past 18 years. Examinations were made by 49 different observers with an average of eight different observers per patient.

The angle of clearance of the left ventricle ranged from 55 to 70 degrees. There was left auricular enlargement in 98 patients. Evidence of cardiac chamber enlargement was obtained in 74 patients although murmurs indicative of valvular deformity had regressed in 28 patients and had become uncharacteristic in 46.

It is concluded that fluoroscopic examination in the posterior-anterior and oblique views at specific degrees of rotation is a reliable procedure for detecting cardiac chamber abnormality, and should be included as part of the routine physical examination.

SUMARIO ESPAÑOL

Se presenta una evaluación de 2973 examenes fluoroscópicos seriales a una rotación de grados específicos en 500 sujetos de 2 a 21 años de edad hechos por 35 examinadores diferentes con un promedio de 5 examinadores por paciente. En la posición posterior-anterior, 1 por ciento mostró convexidad del segmento pulmonar. En la posición oblicua anterior derecha 1 por ciento mostró retrodesplazamiento del esofago. El ángulo al cual se franquea el ventrículo izquierdo en la posición oblicua anterior izquierda fué menos de 55 grados en 90 por ciento de los examenes fluoroscópicos. Adicionalmente, se analizaron 1393 examenes fluoroscópicos seriales rutinarios de 100 pacientes con enfermedad reumática cardíaca inactiva de 4 a 48 años de edad. Hubo un total de 49 examinadores y un promedio de 8 por paciente. El ángulo de franqueo del ventrículo izquierdo fué de 55 a 70 grados. Se encontró engrandecimiento del aurículo izquierdo en 98 pacientes. Se concluye que el examen fluoroscópico a una rotación de grados específicos es un procedimiento confiable para encubrir anormalidades de las cámaras cardíacas y se debe incluir como parte de el examen rutinario.

REFERENCES

[1] ELKIN, M., SOSMAN, M. C., HARKEN, D. E., AND DEXTER, L.: Systolic expansion of the left auricle in mitral regurgitation. New England J. Med. **246:** 958, 1952.

[2] SCHWEDEL, J. B.: Clinical roentgenology of cardiac enlargement. Mod. Concepts Cardiovas. Dis. **21:** 120, 1952.

[3] PARKINSON, J.: The radiology of rheumatic heart disease. Lancet **1:** 895, 1949.

[4] WILSON, M. G.: Clinical radioscopic studies of the heart in children. Am. J. Dis. Child. **47:** 750, 1934.

[5] KUTTNER, A. G., AND REYERSBACH, G.: Value of special radiologic procedures in detecting cardiac enlargement in children with rheumatic heart disease. Am. Heart J. **18:** 213, 1939.

[6] WILSON, M. G.: Rheumatic Fever. New York, The Commonwealth Fund, 1940. Chapter 3. P. 401.

Heart Force Effects of Sympathomimetic Amines as a Basis for Their Use in Shock Accompanying Myocardial Infarction

By Peter C. Gazes, M.D., Leon I. Goldberg, Ph.D., and Thomas D. Darby, B.S.

The treatment of 14 patients in severe shock accompanying myocardial infarction with *l*-norepinephrine (Levophed) in some cases and phenylephrine (Neo-Synephrine) in others demonstrated a significantly higher recovery rate with *l*-norepinephrine. Twelve of the patients were in congestive heart failure. Using strain-gage technics in fully conscious, trained dogs, *l*-norepinephrine was shown to produce substantial increments in heart contractile force in addition to its recognized pressor effects. Approximately equipressor doses of Neo-Synephrine under the same conditions had little effect on contractile force. These pronounced differences in heart force effects are presented as a basis for the difference in clinical results.

SYMPATHOMIMETIC (pressor) amines are being widely used for the treatment of shock accompanying myocardial infarction.[1-7] Most investigators advocating the use of such therapy have based its effectiveness on the peripheral vasoconstrictor action of the amines. The present report presents clinical and laboratory evidence that the success of sympathomimetic amine therapy may additionally be based on its effects on heart contractile force. The clinical studies are based on 14 consecutively treated patients in severe shock accompanying myocardial infarction. Approximately half of this group were treated with intravenous infusions of phenylephrine (Neo-Synephrine). The other half received intravenous infusions of *l*-norepinephrine (Levophed). The laboratory studies, designed to measure relative contractile force and arterial pressure changes in unanesthetized dogs, include such determinations following 51 intravenous injections of *l*-epinephrine, *l*-norepinephrine and Neo-Synephrine in three previously operated dogs. These experiments were in essential confirmation of a larger series conducted with vagotomized, open-chest dogs under anesthesia.[8]

1. Clinical Studies

Methods

The 14 patients with myocardial infarction and shock described in this study were the total number of such patients observed by one of us (P. C. G.) during the period June 1950 to April 1953. These patients represented about 10 per cent of all cases of myocardial infarction treated during this period. Diagnosis was made in each case by studies which included serial electrocardiograms. Before therapy was instituted, all patients were in shock for at least one hour, with low blood pressure, ashen color, anxiety, periods of stupor, and cold, moist skin. Blood pressure measurements were obtained by sphygmomanometer at 10 to 30 minute intervals. The systolic pressure was below 80 mm. Hg in each case except one, a known hypertensive, who presented the typical picture of shock but had a blood pressure of 134/90. This patient's preinfarction pressure ranged from 210/100 to 250/150. The shock state of each patient in this study was of such an extent that survival would have been doubtful without treatment. Previous experience with this type of patient indicated about a 90 per cent mortality rate.

Six of the 14 patients were treated with *l*-norepinephrine, seven with Neo-Synephrine and one with both drugs. *l*-Norepinephrine was administered by intravenous drip in a solution containing 4 mg. *l*-norepinephrine and 5 per cent glucose in each liter of distilled water. Neo-Synephrine was administered in the same manner in a concentration of 10 mg. per liter in two cases and 20 mg. per liter in the others. The rate of infusion flow was determined by the level of systolic blood pressure, which was maintained below 120 mm. Hg in each case except the hypertensive patient noted above. The rate of infu-

Table 1.—*Results of Treatment with l-Norepinephrine and/or Neo-Synephrine of 14 Patients with Severe Shock Accompanying Myocardial Infarction*

Name, Age, Diagnosis	No. of Days after Infarction Shock Developed	Hours in Shock before Treatment	Congestive Heart Failure	B.P. before Amine Administration	B.P. response to Amine Administration	Total Amount of Amine and 5% Glucose Solution Administered	Total Hours Treatment of Shock	Arrhythmias Developing During Therapy	Results
N. B. C., w. m., 43; Post. infarct	1	3	+	B.P. imperceptible	85/?	Neo-Synephrine 10 mg. 1000 cc.	6	None	B.P. became imperceptible with Neo-Synephrine. Death occurred during infusion of whole blood.
B. T. B., w. m., 70; Post. infarct	4	1½	−	B.P. imperceptible	100/?	Neo-Synephrine 10 mg. 1000 cc.	24	None	Died 48 hrs. after infusion discontinued
J. D., w. m., 64; Post. infarct	3	2	+	B.P. imperceptible	70/50	Neo-Synephrine 40 mg. 2000 cc.	30	None	Died during infusion
H. K., w. m., 84; Ant. infarct	1	1	+	60/?	80/70	Neo-Synephrine 40 mg. 2000 cc.	24	Vent. premature contractions	Died during infusion
J. K.,* w. m., 50; Post. infarct	1	2	+	70/?	100/80	Neo-Synephrine 40 mg. 2000 cc.	26	None	Died during infusion
J. F. V.,* w. f., 39; Post. infarct	1	2	−	B.P. imperceptible	130/100	Neo-Synephrine 40 mg. 2000 cc.	36	None	Recovered
C. W. P.,* w. m., 54; Ant. & post. infarct	1½	1	+	B.P. imperceptible	90/70	Neo-Synephrine 20 mg. 1000 cc.	10	None	Died 18 hrs. after infusions discontinued
	2	½		B.P. imperceptible	100/70	l-Norepinephrine 2.7 mg. 670 cc.	8	Aur. fibrillation	
	−			110/70	100/70	Neo-Synephrine 2 mg. 200 cc.	2	Aur. fibrillation	
	2½	½		70/?	110/70	l-Norepinephrine 24 mg. 6000 cc.	72	Aur. premature contractions	
	7½	½		B.P. imperceptible	108/70	l-Norepinephrine 4 mg. 1000 cc.	16	None	

J. F., w. m., 69; Post. infarct	1	1	+	70/?	110/85	Neo-Synephrine 40 mg. 2000 cc.	30	Vent. & aur. premature contractions	Died during infusion
J. H., w. m., 46; Post. infarct	2½	12	+	70/?	120/90	l-Norepineph-rine 8 mg. 2000 cc.	18	Aur. premature contractions	Recovered
J. M., w. m., 51; Post. infarct	1	1	+	B.P. imperceptible	120/90	l-Norepineph-rine 8 mg. 2000 cc.	32	None	Recovered
H. B., w. m., 53; Post. infarct	1	1½	+	B.P. imperceptible	120/90	l-Norepineph-rine 12 mg. 3000 cc.	48	Aur. premature contractions	Recovered
J. A., w. m., 48; Post. infarct	1	1	+	B.P. imperceptible	120/80	l-Norepineph-rine 16 mg. 4000 cc.	54	None	Recovered
E. T., w. m., 48; Post. infarct	2	1	+	134/90	175/110	l-Norepineph-rine 4 mg. 1000 cc.	16	None	Recovered
H. L. H.,* w. m., 53; Post. infarct	3	1	+	60/?	140/90	l-Norepineph-rine 32 mg. 8000 cc.	120	None	Recovered

* These cases reported in detail in Case Abstracts.

sion flow ranged from 5 to 100 drops per minute. If the blood pressure remained stable with the slower flow rate, the pressor amine administration was discontinued. If shock recurred, the infusion was restarted.

Oxygen, sedation (morphine or Demerol), antiarrhythmic drugs (quinidine or Pronestyl) and papaverine were used as indicated. Dicumarol was administered to all patients.

Results

The data in table 1 and the representative Case Abstracts summarize the clinical findings. The cases in table 1 are listed in chronologic order. The relatively recent introduction of *l*-norepinephrine for the therapy of shock accompanying myocardial infarction accounts for the exclusive use of Neo-Synephrine in the earlier cases.

Six of the seven patients treated with *l*-norepinephrine had a satisfactory recovery. Immediately after the start of *l*-norepinephrine administration the blood pressure rose and intensity of heart tones increased markedly. The pulse pressure was typically within normal limits. Approximately 1 liter of 5 per cent glucose solution containing 4 mg. of *l*-norepinephrine was infused over a 12 to 18 hour period. The initial infusion rates were 50 to 100 drops per minute and the final rates were usually 5 to 10 drops per minute. It was necessary to maintain the infusion rate for from 10 hours to 5 days in the various patients, before the blood pressure stabilized. Tachyphylaxis was not observed. The patient (C. W. P., see Case Abstracts) who succumbed after *l*-norepinephrine therapy had been initially unsuccessfully treated with Neo-Synephrine. *l*-Norepinephrine successfully raised and maintained the blood pressure in this patient for 48 hours, at which time it appeared stable and the infusion was discontinued. The patient died 18 hours later, apparently from extension of the infarction. In all patients treated with *l*-norepinephrine, congestive heart failure was present at the time of shock, as was evidenced by basilar rales and/or neck and peripheral vein distension. Antecubital venous pressure determinations in one case (H. L. H., see Case Abstracts) revealed a pressure of 232 mm. of blood before the *l*-norepinephrine infusion was

begun. One hour after the start of the infusion the venous pressure had dropped to 180 mm. and there was a clearing of basilar rales. Decreasing or stopping the rate of *l*-norepinephrine flow in this patient caused an immediate rise in venous pressure; increasing the flow again lowered the venous pressure. On the third day, after the start of the infusion the venous pressure of this patient had dropped to 67 mm. and has remained at normal levels.

Only two of the seven patients treated with Neo-Synephrine emerged from shock. These patients (B. T. B. and J. F. V.) were in shock typical of peripheral vascular collapse with no evidence of congestive heart failure. B. T. B. responded to Neo-Synephrine administration with an immediate blood pressure rise from imperceptible levels to a systolic level of 100 mm. Hg; the diastolic level could not be determined. The pressure later stabilized at 120/110 and the Neo-Synephrine infusion was discontinued. The patient succumbed 48 hours after discontinuance of therapy, apparently from extension of the infarction. J. F. V. (see Case Abstracts) responded to Neo-Synephrine therapy and recovered without complications. The other patients treated with Neo-Synephrine were in congestive heart failure. An immediate pressor response was observed in each of these cases, but the pressure failed to stabilize and the patients succumbed despite continuous Neo-Synephrine infusion (typified by case J. K.; see Case Abstracts). Unlike the response to *l*-norepinephrine, the pressor response to Neo-Synephrine was usually characterized by a small pulse pressure.

CASE ABSTRACTS

C. W. P. was a 54 year old white male admitted because of severe substernal pain of 30 minutes duration. On admission his blood pressure was 98/72, and his pulse was regular at 56 per minute. The electrocardiogram revealed an acute posterior infarction. Two hours later the patient was asymptomatic and blood pressure was 128/90. Thirty-four hours after admission, the patient complained of severe substernal pain, vomited and went into shock. The blood pressure was unobtainable for 60 minutes, and respiration was maintained by artificial means on several occasions during this period. Neck and peripheral veins were markedly distended and basilar rales were present. Intravenous infusion of

Neo-Synephrine, 20 mg. per liter of 5 per cent glucose solution, produced an immediate blood pressure response to levels of 90/70. An electrocardiogram taken at this time revealed that the infarction had spread to involve the anterior surface. Despite continuous Neo-Synephrine therapy, the blood pressure gradually declined and was again unobtainable 10 hours after the start of the infusion. Basilar rales did not diminish with Neo-Synephrine therapy and, in fact, became more prominent. When the blood pressure became unobtainable, intravenous infusion of l-norepinephrine, 4 mg. per liter of 5 per cent glucose solution, was begun with an immediate response of blood pressure to 100/70 and an increase in intensity of heart tones. Eight hours later, auricular fibrillation developed. Quinidine dosage was increased. Because of possible implication of l-norepinephrine in the production of this arrhythmia, its administration was discontinued and Neo-Synephrine was substituted. The blood pressure dropped to a systolic level of 70 mm. Hg, and l-norepinephrine infusion was again started with an immediate pressor response to 110/70, in spite of the auricular fibrillation. The arrhythmia reverted to normal sinus rhythm with many premature auricular contractions persisting during the infusion period. The infusion was continued until the third day when the blood pressure was 100/70. For the following two days, the blood pressure remained stable at about 100/70 when suddenly the patient became dyspneic and the blood pressure again became unobtainable. l-Norepinephrine infusion was restarted and the blood pressure rose to 108/70. The infusion was discontinued after 16 hours when the blood pressure appeared stable at 104/70. For the next 18 hours, the blood pressure remained at about this level. At the end of this period, the patient attempted to leave the bed, became cyanotic and died.

H. L. H., a 53 year old white male, was admitted to the hospital because of severe substernal pain with nausea and vomiting. On admission he appeared pale and his skin was cool. The blood pressure was 120/80 and the cardiac rhythm was regular. An electrocardiogram showed an acute posterior infarction. The blood pressure gradually dropped during the following 72 hours to a systolic level of 60 mm. Hg, at which time shock was apparent. Basilar rales were present and the venous pressure was 232 mm. of blood. An infusion of l-norepinephrine was begun and the arterial pressure rose immediately to 140/90. Heart tones improved and signs of congestive failure cleared. Venous pressure at this time was 180 mm. of blood. When the infusion rate of the solution was decreased, the venous pressure rose and dropped immediately when the rate was increased. Blood pressure was maintained between 95/60 and 110/70 during the following five days. Each attempt to discontinue the infusion resulted in a drop in systolic arterial pressure to levels below

70 mm. Hg, until the fifth day, when the blood pressure appeared stable at a level of 95/70. Venous pressure at this time was 67 mm., color was good, heart tones were regular and clear, and there was no evidence of congestive heart failure. An inflammatory reaction observed at the site of the venepuncture was possibly related to infiltration of l-norepinephrine. It completely healed in three days with use of warm packs and penicillin. This patient was discharged after having been asymptomatic for five weeks.

J. F. V., a 39 year old white female, was admitted to the hospital for the third attack of acute myocardial infarction during the past three years. Prior to admission, she developed severe substernal pain and convulsions, and collapsed. At home and on admission, her skin was cold and clammy, pulse was not present and blood pressure was unobtainable. Heart tones were not audible and only faint breath sounds were present. The patient was unresponsive. There was no evidence of congestive heart failure. An electrocardiogram showed right bundle branch block with an old anterior and a fresh posterior infarction. Infusion of Neo-Synephrine, 20 mg. per liter of 5 per cent glucose solution, produced an immediate rise of blood pressure to 130/100. The heart tones became faintly audible. In three hours the blood pressure appeared stable at levels of approximately 110/78. Ten hours later, the blood pressure dropped to 90/52 and the infusion rate was increased to 50 drops per minute with a pressor response to 116/76. The infusion was completed in 18 hours and another such 1000 cc. infusion was completed during the next 18 hours. At the completion of the second infusion, the blood pressure was 100/68 and remained at similar levels for the next 30 days without further Neo-Synephrine infusions, and the patient was discharged.

J. K., a 50 year old white male, was admitted to the hospital because of severe substernal pain radiating down both arms. His skin was cold and clammy, and he appeared very pale. Heart tones were faint. An electrocardiogram showed an acute posterior infarction with a few premature ventricular contractions. Initially, the blood pressure was 100/60, but 24 hours later it had dropped to a systolic level of 70 mm. Hg, and the patient was in shock with signs of congestive heart failure. An infusion of Neo-Synephrine was begun resulting in an immediate rise of blood pressure to 100/80. Blood pressure remained at this level for several hours. The patient, however, became dyspneic and had more basilar congestion. Ventricular premature contractions were controlled by Pronestyl. Twenty-four hours later, in spite of the Neo-Synephrine infusion, his blood pressure had gradually dropped to 60/50 with reappearance of shock. During the next 30 minutes, the pressure became unobtainable; the patient became cyanotic and expired.

2. Laboratory Studies

Methods

Three trained, mongrel dogs weighing between 10 and 15 Kg. were used in these studies. A metal encased strain gage arch was sutured to the anterior aspect of the right ventricle of each dog for the measurement of heart contractile force. The operation was performed with aseptic technic under pentobarbital anesthesia and with positive pressure respiration using room air. Description of the strain gage arch[9] and the physiologic factors governing its use[10] have been reported in detail. Clinical implica-

Before drug administration, a 15 minute control period with steady contractile force, diastolic and systolic pressure readings was obtained. The sympathomimetic amines were injected rapidly intravenously usually in the following order and in the following doses: *l*-epinephrine (as the bitartrate), 0.001 mg. per kilogram, *l*-norepinephrine (as the bitartrate) 0.001 mg. per kilogram and Neo-Synephrine hydrochloride, 0.015 mg. per kilogram Mephentermine (Wyamine), 1.00 mg. per kilogram and Vasoxyl, 0.10 mg. per kilogram, were also included in some of the experiments. Each amine was administered in a dose calculated to produce an

TABLE 2.—*Effects of Sympathomimetic Amines on Heart Contractile Force, Arterial Blood Pressure and Heart Rate of Unanesthetized Dogs*

Drug	Dose mg./kg.	Number of Dogs	Number of Injections	Postoperative Days Drug Administered	Av. Increment in Contractile Force % of control values	Av. Diastolic B.P. Increment mm. Hg	Av. Systolic B.P. Increment mm. Hg	Av. Heart Rate Change beats/min.
l-Epinephrine	.001	3	20	1st to 8th	128	47	65	−3
l-Norepinephrine	.001	3	17	1st to 8th	151	53	67	−38
Neo-Synephrine	.015	2	14	1st to 8th	15	63	58	−19
Vasoxyl	.100	1	2	4th & 5th	10	50	60	−40
Wyamine	1.000	1	4	4th, 5th, 7th & 8th	107	78	97	+25

tions of studies conducted with the strain gage arch have been presented.[11] While the animals were under anesthesia, polyethylene tubes (inside diameter 0.047 inch) were inserted and tied into an exposed femoral artery and vein for pressure measurements and drug injections. The tubings were filled with Ringer-Locke solution containing heparin (10 U.S.P. units per cubic centimeter) and were sealed by twisting and tying with thread. The incisions were closed and the tubings were placed in metal cans sutured to the skin and heavily taped to prevent interference by the animals. The animals recovered from the anesthesia within six hours and were ambulatory in about 12 hours.

The first experiments were conducted 18 to 24 hours after the operation. The unanesthetized animals were placed on dog boards, gently restrained and petted continuously. Heart contractile force was recorded through a Brush Universal Analyzer (B1-320). Diastolic and systolic femoral pressures were recorded through a Statham Transducer and another Brush Analyzer. The output from both analyzers was recorded synchronously by a two channel Brush ink-writing oscillograph (B1-202). A syringe filled with heparinized Ringer-Locke solution and provided with a two-way stopcock was attached to the venous tubing. All drug injections were made through this tubing, thus eliminating excitement of the animal resulting from venepuncture. Frequent placebo injections of Ringer-Locke solution in approximate volume of the administered drugs were made in each experiment.

approximately equivalent diastolic pressure increment. In one dog, on the third postoperative day, *l*-norepinephrine was infused intravenously by use of a special constant rate infusion pump at rates of 0.010 mg. per kilogram and 0.012 mg. per kilogram per minute. Neo-Synephrine was infused similarly into the same dog on the following day at the rate of 0.20 mg. per kilogram per minute.

Results

Results of the rapid intravenous injections of the amines are summarized in table 2.

After each of the 17 administrations of *l*-norepinephrine, there was a pronounced increment in heart contractile force. This increment averaged 151 per cent of control values. This stimulant response was very similar to that produced by *l*-epinephrine. Neo-Synephrine, however, produced an average increment of only 15 per cent in 14 administrations. This marked difference between the effects of *l*-norepinephrine and *l*-epinephrine on contractile force and the effects of Neo-Synephrine are typically illustrated in figure 1. The results are very similar to those observed in the previous study with open-chest, vagotomized dogs, except that the contractile force increments caused by Neo-Synephrine were relatively

smaller in the present series with unanesthetized animals.

l-Norepinephrine reduced the heart rate considerably more than did *l*-epinephrine, in the present investigation. In the previous

cause of a greater diastolic than systolic pressure increment. The effects produced by *l*-norepinephrine and *l*-epinephrine on contractile force and heart rate lasted from about two to four minutes; the hypertensive effect
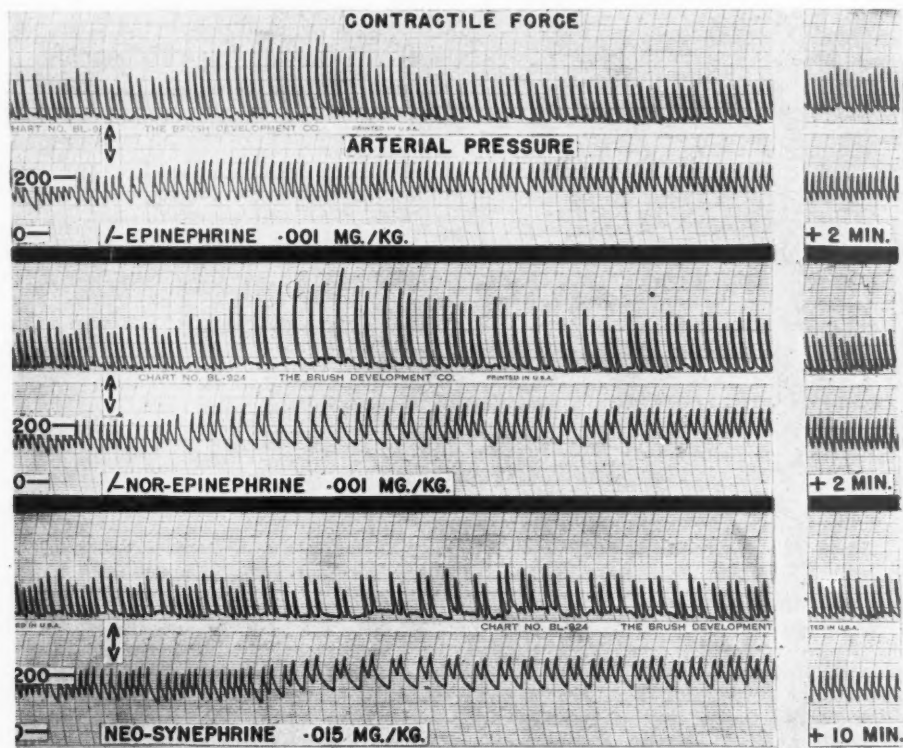

FIG. 1. Effects of *l*-epinephrine, *l*-norepinephrine and Neo-Synephrine on heart contractile force and femoral arterial pressure of an unanesthetized, trained dog. Ventricular contractile force was recorded from a strain gage coil cemented to a metal arch, which had been sutured to the anterior aspect of the right ventricle three days previously. Femoral arterial pressure was recorded by a Statham Transducer attached to polyethylene tubing previously inserted into the artery. The contractile force (upper curves) is directly proportional to the oscillograph lever stroke amplitude. Scales to the left of the arterial pressure tracings (lower curves) indicate millimeters of mercury. Injections were made rapidly through polyethylene tubing previously inserted in the femoral vein.

study with open-chest, vagotomized dogs, both amines produced approximately equivalent degrees of tachycardia.

Pressor effects with *l*-norepinephrine and *l*-epinephrine were closely similar, both amines usually producing an increase in pulse pressure, due to a greater systolic than diastolic pressure increment. Neo-Synephrine administration usually resulted in a decreased pulse pressure, be-

generally persisted for about one minute longer than the contractile force or heart rate effects. The blood pressure and heart rate effects produced by Neo-Synephrine usually persisted for 10 to 15 minutes. The duration of the slight contractile force increment produced by Neo-Synephrine was usually two to three minutes less than that of the heart rate and blood pressure effects.

In the experiment in which *l*-norepinephrine was administered by continuous intravenous infusion at a rate of 0.010 mg. per kilogram per minute, the contractile force and the diastolic and systolic pressures began increasing within two minutes after the infusion was begun. The heart rate began to drop during the same period. At the end of 10 minutes, the contractile force had increased to levels approximately 95 per cent above control values, the diastolic pressure about 20 mm. and the systolic pressure about 50 mm. above control values. The rate had decreased to a level 50 beats per minute below control. These levels remained approximately constant for the final five minutes of the infusion. About five minutes after the infusion was discontinued, contractile force and pressure values had returned to control levels. The heart rate, however, was still 30 beats per minute below control. The infusion was then started again and maintained at a slightly faster rate, 0.012 mg. per kilogram per minute. The response was similar to that of the first infusion, contractile force stabilizing in 10 minutes at levels about 100 per cent above control values, diastolic pressure 30 mm. above control and systolic pressure 65 mm. above control. The rate dropped 10 beats per minute slower than in the previous infusion. These levels were again maintained for five minutes before the infusion was discontinued. All values again returned to control levels in about five minutes, except heart rate which remained 40 beats per minute below control values.

On the following day, Neo-Synephrine was similarly infused into this same dog. The concentration of Neo-Synephrine solution was 0.020 mg. per kilogram per cubic centimeter, and the rate of infusion was 1 cc. per minute. Within two minutes, the diastolic pressure rose 70 mm., the systolic pressure 50 mm.; the contractile force decreased about 25 per cent. In 10 minutes, the diastolic and systolic pressures were at approximately the same high levels and the contractile force had risen to control levels. The infusion was discontinued 15 minutes after it was started. Systolic and diastolic pressures returned to control levels in approximately 15 minutes. There was no further change in contractile force. There was little change of rate during this experiment.

The four administrations of Wyamine and the two administrations of Vasoxyl indicated that the effects produced by these amines on the contractile force in unanesthetized dogs were similar to those reported for the open-chest series. Wyamine produced a pronounced increment in contractile force, averaging 107 per cent of control values and lasting for approximately 15 minutes. Vasoxyl produced little effect on heart contractile force.

DISCUSSION

The problem of shock accompanying myocardial infarction has been comprehensively studied and reviewed by several investigators in recent years.[1, 12, 13] The conclusion of these investigators has been that the shock is the result of one or a combination of the following factors: (1) failure of the heart as a pump and (2) peripheral vascular collapse with a resultant further decrease in coronary flow. Digitalis has been advocated for shock primarily of the first type, and pressor amines, intra-arterial, and intravenous infusions for the second type. Recently, Fink, d'Angio and Biloon[6] have differentiated these two types of shock on the basis of determinations of forearm venous pressure.

Results of the present investigation demonstrate that although *l*-norepinephrine is generally classified clinically as predominantly a pressor amine, it also has a powerful augmenting action on the contractile force of the heart and may thus be beneficially used in shock of either of the above types. Effects considered to be due to increase of contractile force were observed clinically in seven patients described in this report, in whom there were evidences of congestive heart failure in addition to shock. In these patients, there was an almost immediate clearing of pulmonary congestion, increase in intensity of heart tones, increase in pulse pressure and decrease of distension of the veins of the arms and neck. In one of these patients (H. L. H.) direct measurements revealed a drop in venous pressure to normal values during therapy. Kurland and Malach[2] have also noted the clearing of existing pulmonary edema during *l*-norepinephrine ther-

apy. Digitalis therapy may have been beneficial in the above patients, but digitalis does not exert a pressor effect and has a greater tendency to produce cardiac arrhythmias. Additionally, because of the longer period of action of digitalis, its effects cannot be as readily controlled.

The ability of norepinephrine to increase contractile force has been demonstrated by several investigators in a variety of isolated heart preparations[14-17] and anesthetized animals.[8, 18, 19] The present study confirms these results by use of unanesthetized dogs and further demonstrates that the effect on contractile force is maintained as long as the amine is infused.

The clinical impression that *l*-norepinephrine is predominantly a pressor amine, with little or no cardiac action, appears to have been based mainly on studies in normal and hypertensive individuals in whom *l*-norepinephrine administration either decreased or did not affect cardiac output.[20] More recent studies[21] with anesthetized dogs have shown definite increase in cardiac output with *l*-norepinephrine administration. It should be noted that cardiac output is a resultant of several factors, such as force of the heart, peripheral resistance, and heart rate. As *l*-norepinephrine affects each of these factors in varying degrees, administration of this amine may increase contractile force but may decrease or may not change cardiac output.

Neo-Synephrine appears to fulfill the usual definition of a pressor amine, in that its action is largely peripheral. Although amines of this type may be beneficial in those cases of shock accompanying myocardial infarction with peripheral vascular collapse as the major finding (type 2), they may be actually contraindicated in a major proportion of these patients, that is, in those with shock and congestive heart failure (type 1). This observation is supported by the therapeutic failure of Neo-Synephrine in all patients with congestive heart failure described in the present report. Similar views concerning Neo-Synephrine therapy have been expressed by Fink, d'Angio and Biloon.[6]

The work of Hellerstein, Brofman and Caskey[4] has demonstrated that Wyamine is of value in shock following myocardial infarction. From the previous pharmacologic study[8] and the experiments presented here, it appears that Wyamine has a distinct augmenting effect on contractile force, and the success of this amine may also be related to such action. Vasoxyl, however, has been found to be very similar to Neo-Synephrine and should probably be used only with similar restrictions.

As additional sympathomimetic amines are recommended for use in shock accompanying myocardial infarction, it is apparent that all should not be considered as having similar pharmacologic actions and thus be used interchangeably. A thorough knowledge of both pressor effects and effects on heart contractile force should be obtained before therapy with sympathomimetic amines is attempted.

SUMMARY

1. The treatment of 14 cases of severe shock accompanying myocardial infarction by intravenous infusions of *l*-norepinephrine and/or Neo-Synephrine is described. Twelve of the patients were in congestive heart failure. Six patients in congestive heart failure treated with *l*-norepinephrine recovered. Five patients in congestive heart failure treated with Neo-Synephrine responded with an immediate blood pressure rise, but the pressure failed to stabilize and the patients succumbed despite continuous Neo-Synephrine infusions. Two patients, with no evidence of congestive heart failure, were brought out of shock by Neo-Synephrine. One of these patients recovered, the other died 48 hours after the Neo-Synephrine infusion was discontinued. One patient, treated with both amines, failed to respond to Neo-Synephrine and was later brought out of shock by *l*-norepinephrine. This patient died 18 hours after discontinuance of *l*-norepinephrine therapy.

2. *l*-Norepinephrine was found to produce pronounced increments in heart contractile force, in addition to pressor effects, in unanesthetized, trained dogs. The contractile force increments were of similar magnitude to those produced by *l*-epinephrine. Neo-Synephrine was found to be more predominantly a pressor amine, producing only minimal changes in heart contractile force.

3. The effect on contractile force of the

heart of *l*-norepinephrine is presented as a basis for the high recovery rate observed with this amine in the treatment of shock accompanying myocardial infarction, particularly in those cases with associated congestive heart failure.

ACKNOWLEDGMENTS

SUMARIO ESPAÑOL

El tratamiento de 14 pacientes en estado de choque severo como complicación de infarto del miocardio con *l*-norepinefrina (Levophed) en algunos casos y fenilefrina (Neo-Synephrine) en otros, demostró un promedio de recobro significativamente más alto con *l*-norepinefrina. Doce de los pacientes presentaban decompensación cardíaca. Usando la técnica de medida de esfuerzo en perros conscientes y amaestrados, la *l*-norepinefrina mostró producir incrementos substanciales en la fuerza de contracción cardíaca en adición a sus efectos vasopresores. Dosis aproximadamente equipresoras de Neo-Synephrine bajo las mismas condiciones tuvieron poco efecto en la fuerza de contracción. Estas pronunciadas diferencias en la contracción cardíaca se presentan como una base para la diferencia en resultados clínicos.

REFERENCES

[1] CORDAY, E., BERGMAN, H. C., SCHWARTZ, L. L., SPRITZLER, R. J., AND PRINZMETAL, M.: Studies on the coronary circulation, IV. The effect of shock on the heart and its treatment. Am. Heart J. **37**: 560, 1949.

[2] KURLAND, G. S., AND MALACH, M.: The clinical use of nor-epinephrine in the treatment of shock accompanying myocardial infarction and other conditions. New England J. Med. **247**: 383, 1952.

[3] MILLER, A. J., AND BAKER, L. A.: l-Arterenol (Levophed) in the treatment of shock due to acute myocardial infarction. Arch. Int. Med. **89**: 591, 1952.

[4] HELLERSTEIN, H. K., BROFMAN, B. L., AND CASKEY, W. H.: Shock accompanying myocardial infarction: Treatment with pressor amines. Am. Heart J. **44**: 407, 1952.

[5] LIVESAY, W. R., AND CHAPMAN, D. W.: The treatment of acute hypotensive states with l-norepinephrine. Am. J. M. Sc. **225**: 159, 1953.

[6] FINK, T. R., D'ANGIO, C. J., AND BILOON, S.: Clinical study of shock following myocardial infarction. J.A.M.A. **151**: 1163, 1953.

[7] GOOTNICK, A., AND KNOX, JR., F. H.: Management of shock in acute myocardial infarction. Circulation **7**: 511, 1953.

[8] GOLDBERG, L. I., COTTEN, M. deV., DARBY, T. D., AND HOWELL, E. V.: Comparative heart contractile force effects of equipressor doses of several sympathomimetic amines. J. Pharmacol. & Exper. Therap. **103**: 177, 1953.

[9] BONIFACE, K. J., BRODIE, O. J., AND WALTON, R. P.: Resistance strain gauge arches for direct measurement of heart contractile force in animals. Submitted for publication.

[10] COTTEN, M. deV.: Circulatory changes affecting measurement of heart force *in situ* with strain gauge arches. Am. J. Physiol. **174**: 1953. (Sept.)

[11] WALTON, R. P., AND GAZES, P. C.: The effect of digitalis and other drugs on heart contractile force: Clinical implications. South. M. J. **44**: 418, 1951.

[12] BOYER, N. H.: Cardiogenic shock. New England J. Med. **230**: 226, 256, 1944.

[13] HELLERSTEIN, H. K., AND BROFMAN, B. L.: Treatment of hypotensive states accompanying myocardial infarction. Mod. Concepts Cardiovasc. Dis. **20**: 104, 1951.

[14] MARSH, D. F., PELLETIER, M. H., AND ROSS, C. A.: The comparative pharmacology of the N-alkylarterenols. J. Pharmacol. & Exper. Therap. **92**: 108, 1948.

[15] GARB, S.: Inotropic action of epinephrine, norepinephrine, and n-isopropyl-norepinephrine on heart muscle. Proc. Soc. Exper. Biol. & Med. **73**: 134, 1950.

[16] LU, F. C., AND MELVILLE, K. I.: Effects of noradrenaline on coronary flow and heart contraction, as recorded concurrently on the isolated rabbit heart. J. Physiol. **113**: 365, 1951.

[17] LANDS, A. M., AND HOWARD, J. W.: A comparative study of the effects of l-arterenol, epinephrine, and isopropylarterenol on the heart. J. Pharmacol. & Exper. Therap. **106**: 65, 1952.

[18] LUDUENA, F. P., ANANENKO, E., SIEGMUND, O. H., AND MILLER, L. C.: Comparative pharmacology of the optical isomers of arterenol. J. Pharmacol. & Exper. Therap. **95**: 155, 1949.

[19] MELVILLE, K. I.: Blood-pressure effects of noradrenaline and adrenaline with special reference to their antagonism by ergotoxine and other blocking agents. J. Physiol. **113**: 346, 1951.

[20] GOLDENBERG, M., PINES, K. L., BALDWIN, E. deF., GREENE, D. G., AND ROH, C. E.: The hemodynamic response of man to nor-epinephrine and epinephrine and its relation to the problem of hypertension. Am. J. Med. **5**: 792, 1948.

[21] HELLEMS, H. K., LEIGHT, L., CLIFFORD, G. O., HEINRICH, C., AND SNIDER, T. H.: The effects of nor-epinephrine on the circulatory system. Clinical Research Proc. **1**: 6, 1953.

Respiratory and Circulatory Studies of Patients with Mitral Stenosis

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Sixteen patients with severe mitral stenosis have been studied by means of cardiac catheterization, ventilatory and respiratory tests. A decrease in the oxygen diffusing capacity and an increase in venous admixture were observed in a majority of the cases. The degree of pulmonary arterial and arteriolar abnormality observed in lung biopsies failed to correlate with the pulmonary arteriolar resistances calculated from the hemodynamic data. It is suggested that reversible vasoconstriction plays an important role in the pathogenesis of the pulmonary hypertension associated with mitral stenosis.

THE DEVELOPMENT of effective surgical therapy for mitral stenosis has focused interest on the pathologic physiology of this disease. Careful appraisal of abnormalities in circulatory and pulmonary function of patients with mitral stenosis may help in the proper selection of cases for operation and should aid in evaluating the results of surgery. It has been clearly recognized that with long standing mitral stenosis striking pathologic changes in the lungs are found at autopsy.[1, 2] Intimal thickening of the arteries, hyperplastic arteriolar sclerosis, and dilatation of the capillaries are frequently observed. In addition to vascular lesions, the alveolar walls may be affected by edema, fibrosis, and emphysema.

Extensive hemodynamic studies have been carried out which demonstrate that narrowing of the mitral valve produces hypertension throughout the lesser circulation and often an increased resistance to flow through the pulmonary arterioles.[3-8] However, to date there are few reports of abnormalities in pulmonary function in mitral stenosis and the majority of these have dealt with disturbances in ventilation.[1, 10, 11] Blount and coworkers[12] have recently demonstrated an increased alveolar-arterial oxygen tension gradient in

this disease. The present study was undertaken to extend the investigation of respiratory function in patients with mitral stenosis to include abnormalities in gas diffusion and distribution and to learn whether this information might be correlated with clinical and hemodynamic observations and with pathologic changes found in lung tissue obtained by biopsy.

CLINICAL MATERIAL AND METHODS

Sixteen patients with mitral stenosis of varying clinical severity were studied. None was thought to have significant mitral regurgitation. There were no clinical or roentgenologic data to suggest primary pulmonary disease. The clinical findings are summarized in table 1. All patients were considered sufficiently incapacitated to warrant consideration for surgery. Most of the patients had been on a trial of medical therapy including a low sodium diet, diuretics and digitalis. Complete cardiac catheterization data were obtained in all but two of the patients. Ten of the 16 had finger-fracture valvuloplasty shortly after study. A biopsy of the lung was obtained from the anterior margin of the left upper lobe in each of the operated cases.

The studies were conducted in the postabsorptive state. Ventilatory measurements were carried out with the Benedict-Roth spirometer following the recommendations of Comroe.[13] These were limited to the determination of the vital capacity, maximum breathing capacity, and breathing reserve ratio. The predicted normal values for vital capacity and maximum breathing capacity were calculated using the Baldwin-Cournand formulas.[14]

Heart catheterization was performed in the usual manner. Pressure curves were recorded through a Sanborn electromanometer on a direct-writing Polyvisocardiette. Pulmonary "capillary" pressures were

obtained by the method of Dexter.[15] Samples of expired air were collected for two minutes in a Douglas bag and analyzed for oxygen and carbon dioxide with the Haldane apparatus. At the time of the air collection, samples of arterial blood from the radial artery and of mixed venous blood from the pulmonary artery were drawn simultaneously. Pulmonary arteriolar resistance was calculated by the following formula:

$$P.A.R. = \frac{P.A._M - P.C._M}{C.I.} \times 79.92$$

Where $P.A.R.$ is the pulmonary arteriolar resistance expressed as $dynes\ second\ cm^{-5}\ M^2$, $P.A._M$ is the mean

nomogram of Singer and Hastings.[19] These served as a further check on the direct technic. Studies were usually done with the patient first breathing room air and then 15.5 per cent oxygen in nitrogen. Two patients with obvious arterial oxygen unsaturation while breathing room air were given a higher oxygen concentration (25 per cent) in addition to the low mixture. Standard formulas[20] were used in calculating the values for respiratory function.* The arterial carbon dioxide tension, taken to equal the alveolar carbon dioxide tension, was employed in determining the alveolar oxygen tension and the respiratory dead space. The definition of the latter is expanded to include gas contributions from well ventilated but

TABLE 1.—*Clinical Data**

Subjects, Age in Yrs.	Duration of Symptoms in Yrs.	Exertional Dyspnea	Hemoptysis	Pulm. Edema	Right Ventricular Failure		Electrocardiogram		Cardiac Enlargement by X-ray
					Present	Past	R.V.H.	Auricular Fibrillation	
R. C., 22	1	+	+	+	0	0	0	0	+
F. G., 36	3	+	++	+	0	0	0	0	+
J. P., 30	4	+	+++	0	0	0	0	0	+
A. H., 33	8/12	+	0	+	0	0	0	+	+
F. W., 31	3	+	+	0	0	0	0	0	+
R. S., 29	2	++	++	++	0	0	0	0	+
B. L., 39	5	++	0	0	0	0	0	0	0
H. D., 36	9	++	+++	+++	+	+	+	0	++
L. B., 23	5	++	0	++	0	0	0	0	++
M. S., 43	5	+	0	++	0	0	0	0	++
E. P., 29	2	+++	+++	+++	+	+	+	0	+++
P. P., 42	10	+++	0	++	0	++	+	+	+++
F. L., 32	2	+++	+++	+	0	0	0	0	++
M. V., 32	7	+++	0	++	0	+	0	0	+++
W. J., 35	10	++	+	++	0	0	+	0	++
Je. P., 40	6	+	++	++	0	0	0	0	++

* The patients are arranged in order of decreasing estimated mitral valve area.

Symbols are as follows: + slight, ++ moderate, +++ marked.

pulmonary artery pressure in millimeters Hg, $P.C._M$ is mean pulmonary "capillary" pressure in millimeters Hg, and $C.I.$ is the cardiac index in liters per minute per square meter of body surface area. The area of the mitral valve was estimated by the method of Gorlin and Gorlin.[16] Oxygen and carbon dioxide content were determined by the Van Slyke-Neil manometric method. Oxygen and carbon dioxide tensions were determined directly on arterial blood using the Roughton-Scholander analyzer.[17] Equilibration and reading were carried out in a water bath at a constant temperature of 37 C. Determinations were done in duplicate and results were required to check within 2 mm. Hg. The hematocrit and pH were determined, the latter colorimetrically,[18] for the indirect determination of the gas tensions from the oxygen dissociation curve and the

poorly perfused alveoli (the "dead space like" component).[21, 28]

For the determination of the oxygen diffusing capacity the method of Riley and Cournand was used.[22, 23, 24] This requires that the patient be studied at two distinct levels of oxygenation. It makes possible a differentiation of the alveolar-arterial gradient (the difference in oxygen tension between the alveolar air and arterial blood) into two components: the diffusion gradient, which is the difference in oxygen tension between alveolar air and blood leaving the pulmonary capillary; and the venous admixture gradient, which is the difference in oxygen tension between blood leaving the pulmo-

* Symbols will not be used in the text of the paper. They are included in the tables for ease of reference to other work.

nary capillary and arterial blood. The latter results from mixed venous blood reaching the systemic arterial circulation through anatomically distinct shunts (for example, pulmonary artery–pulmonary vein shunts, thebesian veins) and mixed venous blood perfusing poorly ventilated alveoli (the

gradient per minute). This is a function of the area of diffusing surface and the permeability characteristics of the alveolar membrane.

Four of the patients were studied approximately six months postoperatively using technics identical to those outlined above.

TABLE 2.—*Hemodynamic Data*

Subject	Cardiac Index L./min./sq. M.	Right Ventricular End Diastolic Pressure mm. Hg	Pulmonary Artery Mean Pressure mm. Hg	Pulmonary Capillary Mean Pressure mm. Hg	Pulmonary Arteriolar Resistance dynes sec. cm.$^{-5}$ sq. M.	Calculated Mitral Valve Area sq. cm.
Approx. Normal	3.2	3	12	6	150	4
R. C.	4.1 (4.1)*	6	21 (28)	20	140	2.1
F. G.	3.4 (2.9)	4	20 (23)	15	140	1.7
J. P.	3.2 (2.8)	5	18 (23)	18 (20)	150	1.5
A. H.	3.4 (4.2)	5	23 (25)	17	90	1.4
F. W.	3.0 (2.8)	0	25 (29)	22	130	1.1
R. S.†	4.2 (3.7)	5	35 (38)	30	110	1.1
B. L.	3.5 (2.6)	0	40 (40)	25	345	1.0
H. D.	3.6 (4.2)	0	37 (48)	26	260	1.0
L. B.	3.7 (3.2)	0	54 (53)	34 (31)	450	0.9
M. S.	3.1 (3.2)	3	35 (38)	26	280	0.9
E. P.	2.4 (2.0)	10	52	28	900	0.9
P. P.	2.4 (2.3)	3	40 (42)	20	660	0.7
F. L.	2.4 (2.4)	4	34 (50)	28	330	0.6
M. V.	1.3 (1.2)	15	56 (57)	33	1440	0.2
W. J.	2.2	5				
Postoperative						
H. D.	3.5 (2.8)	0	16 (22)	13	69	1.5
L. B.	3.8 (3.5)	0	29 (34)	24 (21)	169	1.3
E. P.	2.9 (2.4)	6	45 (50)	24	550	0.8
F. L.	2.5 (2.1)	5	18 (20)	14	128	1.1

* Figures in parentheses are measurements made after breathing 15.5% O_2 for 15 minutes.
† Inspired air 25% O_2 instead of room air.

TABLE 3.—*Ventilatory Data*

Subjects	R. C.	F. G.	J. P.	A. H.	F. W.	R. S.	B. L.	H. D.	L. B.	M. S.	E. P.	P P.	F. L.	M. V.	W. J.	Je. P.
Vital Capacity % Pred	91	90	90	86	100	55	80	60 (66)	80 (90)	86	79 (67)	71	85 (82)	77	85	62
Maximum Breathing Capacity % Pred	100	87	76	58	74	39	42	49 (58)	71 (81)	79	92 (79)	66	58 (71)	45	77	47
Breathing Reserve Ratio	94	92	92	84	88	89	77	80 (77)	89 (93)	87	85 (89)	82	88 (91)	77	90	83

Figures in parentheses are findings postoperatively.

"venous admixture like" component).[21, 28] The mean alveolar-capillary oxygen tension gradient is derived in this process of differentiation. The oxygen diffusing capacity is the oxygen consumption divided by this gradient (or, in other words, oxygen diffused per millimeter of mercury of mean alveolar-capillary

PREOPERATIVE RESULTS

Hemodynamic Data. Certain information of interest was obtained from cardiac catheterization studies (table 2). The cardiac index was decreased in five cases and normal in the

TABLE 4.—*Minute Volume of Ventilation, Tidal Volume, Oxygen Consumption, Respiratory Quotient, and Alveolar Oxygen Tension*

Subject	O₂ Tension insp. gas PIO₂ mm. Hg	Ventilation min. vol. VE L./sq. M. BTPS	Tidal Volume VT cc. BTPS	O₂ Consumption V̇O₂ cc./min./sq. M. STPD	Respiratory Quotient	O₂ Uptake per liter vent.	Effective Alv O₂ tension PAO₂ mm. Hg
R. C.	149	4.06	332	134	.74	40.7	105
	111	4.37	335	109	.90	30.0	75
F. G.	149	4.38	908	154	.79	42.5	106
	110	4.65	668	141	.83	36.9	69
J. P.	150	4.41	511	132	.93	36.0	110
	111	4.18	548	130	.92	37.2	69
A. H.	150	6.16	629	173	.78	33.6	104
	112	6.63	599	182	.83	32.6	72
F. W.	148	6.00	542	171	.89	34.7	112
	109	6.10	500	151	.85	30.2	63
R. S.	184*	5.32	532	150	.76	33.5	151
	113	6.70	462	144	.92	25.9	80
B. L.	150.5	5.26	477	139	.84	31.7	111
	110.5	5.20	408	126	.87	29.0	73
H. D.	158	5.22	370	151	.70	35.2	114
	110	6.36	379	157	.84	30.0	72
L. B.	149	4.97	467	152	.73	36.9	99
	111	5.40	497	137	.86	30.0	75
M. S.	150	5.28	417	134	.86	30.5	112
	111	5.34	478	115	.95	25.9	65
E. P.	148	7.93	548	162	.71	24.7	108
	111	7.58	489	135	.87	21.3	77
P. P.	149	6.23	444	136	.89	26.2	105
	111	6.55	650	127	.99	23.6	73
F. L.	149	3.87	715	115	.90	35.5	112
	111	4.00	628	113	.91	33.9	74
M. V.	151	5.88	435	146	.72	29.7	108
	112	7.10	426	124	.85	21.0	76
W. J.	151	4.27	573	128	.77	35.5	104
	112	4.23	568	106	.84	29.8	68
Je. P.	182*	4.08	274	125	.75	36.7	132
	112	4.61	309	131	.89	34.1	69
Postoperative							
H. D.	150	7.16	704	159	.93	26.6	118
	110	5.16	505	122	1.01	28.3	79
L. B.	151.5	3.35	700	116	.83	41.3	115
	111.8	3.26	468	108	.88	39.4	74
E. P.	149	5.72	455	154	.76	31.9	104
	110.7	5.14	512	126	.83	29.6	70
F. L.	151	3.67	505	116	.74	37.7	112
	112.5	3.46	439	104	.86	32.5	79

* 25% O₂ in nitrogen.

remainder. The pulmonary artery and pulmonary "capillary" mean pressures were elevated in all. Pulmonary arteriolar resistance was significantly elevated in eight of the cases. The estimated mitral valve area ranged between 0.2 and 2.1 cm.² Two patients had high right ventricular end-diastolic pressures consistent with right ventricular failure.

Ventilatory Data (table 3). The vital capacity was slightly to moderately reduced in 12 patients. The maximum breathing capacity was moderately to considerably reduced in

1? cases. As expected, the breathing reserve (the maximum breathing capacity minus the minute ventilation at rest) was reduced in those cases showing a decreased maximum breathing capacity. The breathing reserve ratio (the per cent of maximum breathing capacity not used at rest) was slightly to moderately reduced in 12 patients.

Respiratory Data. The data are presented in tables 4, 5, 6 and 7. The minute volume of ventilation was elevated in every case with the patient breathing room air. There was usually a slight increase when the low oxygen mixture was used. The arterial oxygen saturation with the patient breathing room air was somewhat less (ranging from 80 to 94 per cent) than the normal values for this laboratory (95 to 97 per cent), with the exception of six cases. The expected fall in arterial oxygen saturation occurred while breathing the low oxygen mixture. Hyperventilation was indicated in eight cases by the finding of a low arterial carbon dioxide tension. It was also reflected in the elevated pH values frequently observed.

The alveolar-arterial oxygen tension gradient was elevated in all but two cases breathing room air. The *mean* effective alveolar-capillary oxygen tension gradient was elevated in all cases and markedly so in 10. The oxygen diffusing capacity was decreased in all but two cases in which it approached the lower limit of normal.

The venous admixture, expressed as per cent of cardiac output, was considerably increased in nine and slightly increased in three cases. The respiratory dead space (that portion of tidal volume not actively participating in gas exchange), expressed as per cent of tidal volume, was slightly to moderately increased in six cases. The remaining portion of the tidal volume, the effective alveolar ventilation, tended to be high in those cases with hyperventilation and normal dead space. It was slightly reduced in two cases with increased dead space and in one with normal dead space.

Lung Biopsies. In 10 cases lung biopsies were obtained. The most significant abnormalities are summarized in table 8. Pathologic

vascular changes were invariably present. In addition to varying degrees of capillary dilatation, intimal proliferation and fibrosis were

TABLE 5.—*Arterial and Mixed Venous Blood Data*

Subject	Art. Blood O_2 Sat. SaO_2	Mixed Venous Blood O_2 Sat. $S\bar{V}O_2$	Arterial O_2 Tension PaO_2 mm.Hg	Arterial CO_2 Tension $PaCO_2$ mm.Hg	Arterial pH
R. C.	96	73	82	34	7.44
	84	67	47	33	7.47
F. G.	94	68	75	35	7.43
	89	62	56	35	7.45
J. P.	96	69	99	38	7.44
	91	65	60	38	7.42
A. H.	93	66	65	37	7.47
	84	62	43	34	7.52
F. W.	94	54	85	33	7.45
	87	51	55	40	7.40
R. S.	96	70	92	27	7.55
	86	60	50	30	7.50
B. L.	97	70	85	34	7.47
	92	61	59	33	7.50
H. D.	92	67	70	33	7.43
	80	56	44	33	7.50
L. B.	89	62	58	38	7.43
	80	53	41	32	7.50
M. S.	97	70	90	33	7.50
	87	64	50	34	7.50
E. P.	93	58	70	30	7.42
	85	49	48	30	7.42
P. P.	93	61	70	38	—
	88	52	50	38	—
F. L.	94	65	73	34	7.46
	83	55	44	34	7.48
M. V.	90	36	57	33	7.47
	79	32	40	31	7.50
W. J.	97	63	93	37	—
	82	—	46	38	7.43
Je.P.	94	—	87	40	7.45
	84	—	47	39	7.45

Postoperative					
H. D.	97	70	83	30	7.55
	94	69	59	31	7.55
L. B.	99	78	102	31	7.50
	91	69	59	34	7.50
E. P.	96	67	87	34	7.45
	89	60	55	34	7.48
F. L.	97	70	93	29	7.53
	95	69	72	29	7.52

frequently noted in the arteries and arterioles. There was slight thickening of the alveolar septa in 7 of the 10 cases, fibrosis of the alveolar

TABLE 6.—*Differentiation of the Alveolar–Arterial Gradient.*

Subject	Effect Alv. O₂ Tension PeA$_{O_2}$ mm. Hg	Effect Cap. O₂ Tension Pe$_{CO_2}$ mm. Hg	Art. O₂ Tension Pa$_{O_2}$ mm. Hg	"Effective" Cap. Blood-Mixed Venous Blood Sat. Difference Sc$_{O_2}$−S$\bar{v}_{O_2}$	Effect Alv.-Art. Tension Gradient PeA$_{O_2}$−Pa$_{O_2}$ mm. Hg	Final Effect Alv.-Cap. O₂ Tension Gradient PeA$_{O_2}$−Pe$_{CO_2}$ mm. Hg	Effect Cap.-Art. O₂ Tension Gradient Pe$_{CO_2}$−Pa$_{O_2}$ mm. Hg	Mean Effect Alv.-Cap. O₂ Tension Gradient PeA$_{O_2}$−$\bar{P}_{CO_2}$ mm. Hg	Venous Admixture as % Cardiac Output Qva/Qt×10
				Preoperative					
R. C.	105	97	82	25	23	8	15	(37)	7
	75	49	47	19	28	26	2	37	(7)
F. G.	106	106	75	30	31	<½	31	(16)	14
	69	67	56	31	13	2	11	16	(14)
J. P.	110	110	99	29	11	<½	11	(22)	3
	69	63	60	25	9	6	3	22	(3)
A. H.	104	101	65	22	39	3	36	(33)	20
	72	52	43	26	29	20	9	33	(20)
F. W.	112	112	85	44	27	<½	27	(15)	7
	63	62	55	39	8	1	7	15	(7)
R. S.	151*	151	92	28	59	<1	59	(38)	13
	80	58	50	30	30	22	8	38	(13)
B. L.	111	111	85	28	26	<½	26	(25)	9
	73	67	59	32	14	6	8	25	(9)
H. D.	114	112	70	31	44	2	42	(33)	19
	72	53	44	32	28	19	9	33	(19)
L. B.	99	93	58	36	41	6	35	(38)	25
	75	52	41	35	34	23	11	38	(25)
M. S.	112	112	90	28	22	<½	22	(22)	8
	65	55	50	25	15	10	5	22	(8)
E. P.	108	106	74	40	34	2	32	(39)	11
	77	56	48	39	29	21	8	39	(11)
P. P.	105	104	70	37	35	1	34	(29)	15
	73	61	50	39	23	12	11	29	(15)
F. L.	112	109	73	33	39	3	36	(37)	15
	74	51	44	32	30	23	7	37	(15)
M. V.	108	106	57	62	51	2	49	(45)	17
	76	52	40	56	36	24	12	45	(17)
W. J.	104	102	93	—	11	2	9	(33)	3
	68	47	46	—	22	21	1	33	(3)
Je. P.	132*	132	87	—	45	<½	43	(30)	12
	69	53	47	—	22	16	6	30	(12)
				Postoperative					
H. D.	118	118	83	28	35	<½	35	(28)	12
	79	70	59	26	20	9	11	28	(12)
L. B.	115	115	102	20	13	<½	13	(25)	5
	74	62	59	23	15	12	3	25	(5)
E. P.	104	104	87	31	17	<½	17	(24)	7
	70	61	55	32	15	9	6	24	(7)
F. L.†	112	112	93	28	19	<½	19	—	6
	79	—	72	26‡	7	—	—	—	—

* Inspired gas 25% O₂.

† Diffusing capacity not determined because PA$_{O_2}$ − Pa$_{O_2}$ too small at low O₂ level.

‡ Calculated on basis of P$_{CO_2}$ being 79 mm. Hg.

walls in three, and emphysema in five (figs. 2 and 3).

POSTOPERATIVE RESULTS

The four patients studied postoperatively (H. D., L. B., F. L., and E. P.) all reported considerable relief of symptoms. All had greatly increased exercise tolerance. The noteworthy features of their second study are outlined briefly below.

Hemodynamic Changes. In one patient

(E. P.) there was almost no change in the hemodynamic findings postoperatively. In the other three patients there were notable reductions in pulmonary artery pressure (average fall of 50 per cent), in pulmonary capillary pressure (average fall 43 per cent), in pulmonary arteriolar resistance (average fall 74 per cent), and increases in the estimated mitral valve area (average rise 63 per cent).

Respiratory Changes. Hyperventilation was still evident in H. D. and E. P. The arterial carbon dioxide tension was low in all, as it tended to be preoperatively. The pH values were increased to the alkalotic range in three. In the absence of hyperventilation in L. B. and F. L., these results cannot be explained adequately. There was a significant rise in the arterial oxygen tension and saturation in all. The saturation preoperatively was normal only in F. L. In contrast to the preoperative study, there was a relatively slight fall in arterial oxygen saturation with the patient breathing the low oxygen mixture, but an adequate fall in oxygen tension occurred in all except one patient. The high pH contributed to the maintenance of good saturation even with the low oxygen tensions.* In F. L. the fall in oxygen tension was not great enough to permit quantitative determination of the diffusing capacity which can be presumed to be normal. Venous admixture, previously elevated in the four cases, returned to normal in three. It remained moderately increased in H. D. Respiratory dead space preoperatively was slightly elevated in E. P. only, and this returned to normal. The value obtained for the dead space postoperatively in L. B. must be attributed to analytical error.

DISCUSSION

The hemodynamic data are characteristic of severe mitral stenosis in the majority of patients studied. Only 4 of 13 patients had an estimated mitral valve area greater than 1.2 sq.cm. In several of the patients the "pulmonary capillary" pressure was elevated to

* A glance at the oxygen dissociation curve makes this pH effect clear. For example, H. D. with an oxygen tension of 59 mm. Hg at the low level was still 94 per cent saturated at pH 7.55. With a tension of 59 mm. Hg at pH 7.40, saturation is 89 per cent.

TABLE 7.—*Dead Space. Effective Alveolar Ventilation and Circulation. Oxygen Diffusing Capacity*

Dead Space as % of Tidal Air $\dot{V}D/\dot{V}T \times 100$	Effect Alv. Vent. $\dot{V}^eA$ L./min./M.³	Effect Alv. Circ. $\dot{Q}^cc$ L./min./M.²	O₂ Diffusing Capacity DO_2 cc./min./M.²/mm.Hg
Preoperative			
Normal 30	2.6	2.9	10*
R. C. 16 (21)†	2.6	3.8	3
F. G. 24 (28)	3.0	2.9	9
J. P. 24 (24)	2.8	3.1	6
A. H. 37 (32)	3.1	2.8	6
F. W. 21 (42)	3.9	3.2	10
R. S. 19 (29)	3.6	3.7	4
B. L. 30 (29)	3.0	3.2	5
H. D. 29 (29)	2.7	2.9	5
L. B. 35 (30)	2.5	2.8	4
M. S. 27 (34)	3.0	2.9	6
E. P. 35 (43)	3.3	2.1	4
P. P. 40 (46)	2.7	2.0	5
F. L. 23 (24)	2.6	2.0	3
M. V. 38 (43)	2.7	1.1	3
W. J. 36 (41)	2.3	2.1	3
Je. P. 27 (23)	2.0	—	5
Postoperative			
H. D. 25 (21)	4.2	3.1	4
L. B. 7 (12)	2.7	3.6	4
E. P. 29 (36)	2.9	2.7	5
F. L. 15 (16)	2.6	2.4	—

* From Riley.[28]

† Figures in parenthesis indicate dead space per cent at low O₂ levels.

TABLE 8.—*Lung Biopsies*

Subjects	Arterial Disease		Alveolar Septal Thickening	Alveolar Septal Fibrosis	Emphysema
	Large Vessel	Small Vessel			
F. W.	++	++	+	0	0
B. L.	++	++	0	0	+
H. D.	+	++	+	0	+
L. B.	++	++	+	0	0
M. S.	+	0	+	0	+
E. P.	+	++	+	+	+
P. P.	++	0	0	0	+
F. L.	0	+	+	+	0
M. V.	++	+	+	+	0
W. J.	+	+	0	0	+

levels at which pulmonary edema may occur (30 mm. Hg). Although variable, the pulmonary arteriolar resistance was found to increase with the severity of the mitral stenosis.

Thus, the seven patients with the smallest estimated mitral valve areas were the patients with significantly elevated pulmonary arteriolar resistances. In the same group of patients the resting cardiac index tended to be low.

The ventilatory data showed a decrease in vital capacity and an even more striking reduction in maximum breathing capacity. This has also been pointed out by other workers. The most severe and longstanding cases are most likely to show alterations in these values.
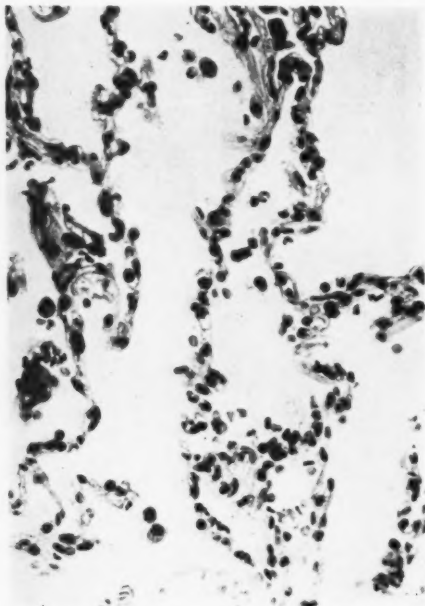
FIG. 1. Normal lung. (200×; H. E. Stain)

Although the breathing reserve ratio was reduced in 11 cases, in none of them was the ratio lowered to values which are usually associated with dyspnea (less than 70). All of our patients had dyspnea on exertion, and a few were dyspneic at rest. The impairment of ventilatory function found in these cases seems inadequate to account for their respiratory disability. However, it should be noted that in far advanced cases marked ventilatory deficiency has been demonstrated.[25] The reduction in ventilatory function in patients with mitral stenosis may be due to such factors as an increased blood content in the lungs,

fibrosis, emphysema or atelectasis. The disproportionate decrease in maximum breathing capacity as compared with the vital capacity* is probably due to an increase in lung stiffness.

More significant changes were noted in the respiratory function studies. The most important findings were a reduction in the diffusing capacity for oxygen in 14 of the 16 cases and an increase in the venous admixture in 12. A low diffusing capacity may be due to a reduction in the total area of gas exchange interface or to an increased resistance to diffusion across it. The latter factor is probably very important. Although the degree of alveolar septal thickening found in 7 of the 10 lung biopsies is not too impressive, it is reasonable to believe that the alveolar walls are probably less permeable than the normal alveolar membrane (fig. 1). In some cases, this thickening results from edema and increased ground substance. In others, in addition to these changes, there is an increase of collagen. However, the structural changes seem hardly severe enough to account for the extremely low diffusing capacity found in some cases. Here other factors may be operative in effectively decreasing the total area of gas exchange interface. Changes in the capillary bed must then be considered. There may be actual reduction in the number of capillaries as suggested by Parker and Weiss.[1] In addition, from a functional standpoint, the low cardiac output and increased pulmonary arteriolar resistance found in the more severe cases would tend to considerably reduce the number of effectively perfused capillaries. There is evidence that increased pulmonary arteriolar resistance is in part due to vasoconstriction (see below). Thus, probably both organic and functional changes are important in causing the low diffusing capacities found in this group of cases.

It is of interest to note that those patients most severely restricted by their disease clinically usually had the lowest diffusing capacity.

The increased values for respiratory dead space and venous admixture in many of the cases indicate abnormalities in ventilation-

* Otherwise expressed as an air velocity index less than unity.[26]

perfusion relationships. The increased dead space found in six cases was not of high order. The low cardiac indexes found in five of the cases causing poor perfusion of ventilated alveoli could cause an increase in "dead space like" effect.

The second important abnormality found, increase in venous admixture, is difficult to interpret. It is not possible to say whether this was due to an increase in the true venous admixture (through anatomic shunts) or the

FIG. 2. Biopsy of L. B. (200×; Periodic acid-Schiff stain.) Thickening of the alveolar walls without fibrosis.

"venous admixture like" component (by perfusion of poorly ventilated alveoli). Possibly both factors are important. The former might be augmented by the high pulmonary artery pressure, tending to increase the amount of flow through normal shunts.[27] The latter may have been increased by such factors as atelectasis or intra-alveolar edema.*

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* It should be noted that if error in the determination of the arterial carbon dioxide tension results in values which are too low, the alveolar oxygen tensions calculated therefrom will be falsely high. This would result in a larger alveolar-arterial oxygen tension gradient and an increased venous admixture.

Studies carried out approximately six months postoperatively revealed several important changes from preoperative measurements. As would be anticipated, an increase in mitral valve area resulted in a decrease in pulmonary capillary and pulmonary artery pressures. The striking reduction in pulmonary arteriolar resistance was of particular interest. Studies on a larger group of cases of mitral stenosis operated on in this hospital have shown no consistent correlation between the calculated

FIG. 3. Biopsy of E. P. (200×; H. E. Stain.) Thickening and slight fibrosis of the alveolar walls and emphysema are evident. Note large number of "heart failure" cells.

pulmonary arteriolar resistance and the degree of pulmonary arteriolar disease in lung biopsies. This is illustrated by cases M. V., and P. P. where there was a high pulmonary arteriolar resistance with little or no morphologic change in the pulmonary arterioles. It has been a common assumption that increased pulmonary arteriolar resistance represents irreversible vascular damage. However, the lack of correlation between pulmonary arteriolar resistance and the degree of pulmonary vascular abnormality seen in lung biopsies suggests

that vasoconstriction may be the most important factor in increasing resistance to blood flow through the lung. The marked reduction in calculated pulmonary arteriolar resistance following operation lends support to this concept. Postoperatively the patients showed pronounced clinical improvement, and three of the four cases studied had a significant increase in the estimated mitral valve areas expressed as per cent of the preoperative areas. However, following valvuloplasty, the estimated mitral valve area ranged from 0.84 to 1.5 sq. cm., values which have been considered characteristic of an important degree of mitral stenosis.[5]

The respiratory function studies in this group showed a significant rise in arterial oxygen saturation and in arterial oxygen tension. This can in large part be accounted for by the sharp reduction in venous admixture which was observed postoperatively. Such a decrease in the venous admixture may have resulted from a lowering of pressure gradient between pulmonary artery and pulmonary veins, thereby reducing blood flow through anatomic shunts. There was no significant change in the oxygen diffusing capacity at rest. As suggested by Riley, however, the determination of the maximum diffusing capacity during exercise may demonstrate significant change commensurate with the degree of clinical improvement in these patients postoperatively. A larger group of cases restudied following a longer interval after operation will be necessary in order to determine to what extent the respiratory abnormalities are due to changes in the lung which are reversible.

SUMMARY AND CONCLUSIONS

A. Preoperative Results

1. Sixteen patients with mitral stenosis have been studied by means of cardiac catheterization, ventilatory and respiratory tests.

2. The hemodynamic data were characteristic of severe mitral stenosis in the majority of cases studied. The patients with the smallest estimated mitral valve areas tended to show the highest pulmonary arteriolar resistances and the lowest resting cardiac outputs.

3. Most of the patients showed a decrease

in vital capacity and in maximum breathing capacity. This, however, seemed inadequate to account for the degree of their respiratory disability.

4. A decrease in the oxygen diffusing capacity and an increase in venous admixture were observed in a majority of the cases. Those patients most severely restricted by their disease clinically usually had the lowest oxygen diffusing capacity.

5. Lung biopsies showed thickening, and at times fibrosis, of the alveolar walls. These structural changes may account for the impairment of oxygen diffusion.

6. The degree of pulmonary arterial and arteriolar abnormality observed in the lung biopsies failed to correlate with the pulmonary arteriolar resistances calculated from the hemodynamic data.

B. Postoperative Results

1. Four of the above patients were studied approximately six months after mitral valve surgery.

2. Three of these patients showed a reduction in the pulmonary artery and "pulmonary capillary" pressures. There was a striking decrease in the pulmonary arteriolar resistances in all. Despite considerable relief of symptoms, the estimated area of the mitral valve was still within the range usually considered indicative of an important degree of mitral stenosis.

3. There was also marked contrast between the observed clinical improvement and the lack of change in the ventilatory measurements.

4. There was no significant change in the oxygen diffusing capacity in three of the patients. The venous admixture fell to normal in three patients and decreased considerably in the fourth. This resulted in an increase in the arterial oxygen saturation and tension.

5. The lack of correlation between morphologic changes in the smaller blood vessels of the lung and the pulmonary arteriolar resistance, together with the pronounced fall in the latter after operation, are of note. They suggest that reversible vasoconstriction plays an important role in the pathogenesis of the pul-

monary hypertension associated with mitral stenosis.

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SUMARIO ESPAÑOL

Diez y seis pacientes con estenosis mitral fueron estudiados por medio de cateterismo cardíaco y pruebas respiratorias y ventilatorias. Un decremento en la capacidad de difusión de oxígeno y un aumento en la mezcla venosa fueron observados en la mayoría de los casos. El grado de anormalidad en las arterias y arteriolas pulmonares observado en biopsias del pulmón no correlacionó con la resistencia arteriolar pulmonar calculada de los datos hemodinámicos. Se sugiere que la vasoconstrición reversible juega un papel importante en la patogénesis de la hipertensión pulmonar asociada a la estenosis mitral.

REFERENCES

1 PARKER, F., JR., AND WEISS, S.: The nature and significance of the structural changes in the lungs in mitral stenosis. Am. J. Path. **12:** 573, 1936.

2 LARRABEE, W. F., PARKER, R. L., AND EDWARDS, J. E.: Pathology of intrapulmonary arteries and arterioles in mitral stenosis. Proc. Staff Meet., Mayo Clinic **24:** 316, 1949.

3 DEXTER, L., GORLIN, R., LEWIS, B., HAYNES, F., AND HARKEN, D.: Physiological evaluation of patients with mitral stenosis before and after mitral valvuloplasty. Tr. Am. Clin. Climat. Assoc. **62:** 170, 1950.

4 GORLIN, R., HAYNES, F. W., GOODALE, W. T., SAWYER, C. G., DOW, J. W., AND DEXTER, L.: Studies of the circulatory dynamics in mitral stenosis. Am, Heart J. **41:** 30, 192, 1951.

5 LEWIS, B., GORLIN, R., HOUSSEY, H., HAYNES, F., AND DEXTER, L.: Clinical and physiological correlations in patients with mitral stenosis. Am. Heart J. **43:** 2, 1952.

DEXTER, L.: Pathologic physiology of mitral stenosis and its surgical implications. Bull. New York Acad. Med. **28:** 90, 1952.

7 ELIASCH, H., WAOLS, G., AND WERKO, L.: The effects of work on the pulmonary circulation in mitral stenosis. Circulation **5:** 271, 1952.

8 LUKAS, D. S., AND DOTTER, C. T.: Modifications of the pulmonary circulation in mitral stenosis. Am. J. Med. **12:** 639, 1952.

9 ALTSCHULE, M. D., ZAMCHECK, M., AND IGLAUER, A.: The lung volume and its subdivisions in the upright and recumbent positions in patients with congestive failure. Pulmonary factors in the genesis of orthopnea. J. Clin. Investigation **22:** 805, 1943.

10 DRINKER, C., PEABODY, F., AND BLUMGART, H. L.: The effect of pulmonary congestion on the ventilation of the lungs. J. Exper. Med. **35:** 77, 1922.

11 MACK, I., GROSSMAN, M., AND KATZ, L.: The effect of pulmonary congestion on distensibility of the lung. Fed. Proc. **6:** 161, 1947.

12 BLOUNT, S. G., JR., McCORD, M. C., AND ANDERSON, L. L.: The alveolar-arterial oxygen pressure gradient in mitral stenosis. J. Clin. Investigation **31:** 840, 1952.

13 COMROE, J. H., JR.: Pulmonary function tests: in Methods in Medical Research. Chicago, Year Book Publishers, 1950. Vol. 2.

14 BALDWIN, E. D., COURNAND, A., AND RICHARDS, D. W., JR.: Pulmonary insufficiency: I. Physiological classification, clinical methods of analysis, standard values in normal subjects. Medicine **27:** 243, 1948.

15 HELLEMS, H., HAYNES, F., AND DEXTER, L.: Pulmonary capillary pressure in man. J. Appl. Physiol. **2:** 24, 1949.

16 GORLIN, R., AND GORLIN, S. G.: Hydraulic formula for calculation of the area of the stenotic mitral valve, other cardiac valves, and central circulatory shunts. Am. Heart J. **41:** 1, 1951.

17 RILEY, R. L., PROEMMEL, D. D., AND FRANKE, R. E.: A direct method for determination of oxygen and carbon dioxide tensions in blood. J. Biol. Chem. **161:** 621, 1945.

18 HASTINGS, A. B., AND SENDRAY, J.: The colorimetric determination of blood pH at body temperature without buffer standards. J. Biol. Chem. **61:** 695, 1924.

19 SINGER, R. B., AND HASTINGS, A. B.: Improved clinical method for estimation of disturbances of acid-base balance of human blood. Medicine **27:** 223, 1948.

20 PAPPENHEIMER, J. R., ET AL.: Standardization of definitions and symbols in respiratory physiology. Fed. Proc. **9:** 602, 1950.

21 RILEY, R. L., AND COURNAND, A.: "Ideal" alveolar air and the analysis of ventilation-perfusion relationships in the lungs. J. Appl. Physiol. **1:** 811, 1949.

22 —, AND —: Analysis of factors affecting partial pressures of oxygen and carbon dioxide in gas and blood of lungs: theory. J. Appl. Physiol. **4:** 77, 1951.

23 —, —, AND DONALD, K. W.: Analysis of factors affecting partial pressures of oxygen and carbon dioxide in gas and blood of lungs. Method. J. Appl. Physiol. **4:** 102, 1951.

[24] DONALD, K. W., RENZETTI, A., RILEY, R. L., AND COURNAND, A.: Analysis of factors affecting partial pressure of oxygen and carbon dioxide in gas and blood of lungs. J. Appl. Physiol. **4:** 497, 1952.

[25] FRANK, R., CUGELL, D. W., GAENSLER, E. A., AND ELLIS, L. B.: Ventilatory functions in mitral stenosis. Proc. New England Cardiovasc. Soc. Nov. 1951.

[26] GAENSLER, F. H.: Air velocity index. A numerical

expression of the functionally effective portio⟨n⟩ of ventilation. Am. Rev. Tuberc. **62:** 17, 195⟨0⟩.

[27] PRINZMETAL, M., ORNITZ, E., SIMKIN, B., AN⟨D⟩ BERGMAN, H.: Arteriovenous anastomosis i⟨n⟩ liver, spleen and lungs. Am. J. Physiol. **152:** 4⟨8⟩, 1948.

[28] RILEY, R. L., RILEY, M. C., AND HILL, H. McD⟨.⟩: Diffuse pulmonary sarcoidosis: diffusing c⟨a⟩pacity during exercise and other lung functio⟨n⟩ studies in relation to ACTH therapy. Bul⟨l.⟩ Johns Hopkins Hosp. **91:** 345, 1952.

Further Studies in High Fidelity Electrocardiography: Myocardial Infarction

By Paul H. Langner, Jr., M.D.

High fidelity electrocardiography employing the cathode ray oscillograph with an expanded time scale reveals considerable high frequency notching, slurring, beading, and other peculiarities not seen in the conventional electrocardiographic records on the same individuals. Although some of these cathode ray records contain components whose frequencies are well in excess of 1000 cycles per second, in this paper a frequency analysis will not be reported but rather the electrocardiograms will be presented as patterns with unique detail that is readily apparent even to the casual observer. Using this technic it was found that 14 of 21 individuals with healed myocardial infarction had a greater incidence of obvious high frequency components in their cathode ray electrocardiograms than was found in a series of 60 normal controls. The possible significance of this finding and the need for further study are discussed.

IN TWO previous papers the technic of high fidelity electrocardiography employing a cathode ray oscillograph and an expanded time scale for the more detailed study of electrocardiographic patterns was described and a summary of our findings in normal individuals was presented.[1, 2] The present paper consists of a report of 21 patients with healed myocardial infarction studied by this technic. This group was compared with a control series of 60 apparently healthy individuals free from any past history, symptoms, or signs of cardiovascular disease. Our purpose in studying patients with healed myocardial infarction and residual diagnostic Q waves in their records was to determine whether such patients having clearly documented heart disease also possessed increased high-frequency detail in the record made by the cathode ray oscillograph, using an expanded time scale. In general, the cathode ray oscillograph records of this abnormal group revealed characteristics not seen in our normal group. There was a noticeable or distinct increase in detail as manifested by high frequency notching, slurring and beading, or bizarre patterns in a majority of the abnormal group. The high frequency components of this additional detail were not revealed by the conventional electrocardiogram.

The use of a considerably expanded time scale in electrocardiography which revealed increased detail has been previously reported by Groedel[3] and Reid and Caldwell.[4] However, they did not use a cathode ray oscillograph. Gilford[5] has used a cathode ray oscillograph and a Fairchild camera for recording electrocardiograms. He observed some increased detail in the tracings but concluded after a limited study that it did not contribute significantly to clinical interpretation. However, Gilford did not establish any high frequency criteria for the differentiation of normal and abnormal individuals. Dunn and Rahm[6] have also used a cathode ray oscillograph and an expanded time scale for electrocardiography. They concluded that when compared with a cathode ray oscillograph, the conventional electrocardiographs tested by them appeared to be inadequate for accurate recording and resulted in definite distortion of the electrocardiographic deflections and loss of fine detail. Although Dunn and Rahm were aware of the increased high frequency detail in their cathode ray oscillograph records, they have not yet published any evaluation of this to the best of our knowledge. Kerwin[7] has concluded that the investigation of frequencies as high as 6400 cycles per second and a paper speed of 500 mm. per second are warranted for research. Thus far he has not evaluated the practical significance of these high frequencies in pathologic processes.

MATERIAL AND METHODS

The high fidelity instrument used in this study consisted of a DuMont Cathode Ray Oscilloscope, type 304-H, using the DC amplifier and a specially built preamplifier.[1] The camera was a Westinghouse Oscilloscope Camera, model ph 33671-1, using Kodak Linagraph paper no. 697. The frequency response curve is substantially flat to 1000 cycles per second. The paper speed was approximately 350 mm. per second in most experiments. The amplification was usually regulated in such a manner that the QRS deflection occupied about two-thirds of the diameter of the cathode ray oscillograph fluorescent screen. This resulted in a standardization of from 2 to 6 cm. = 1 mv. depending on the size of the QRS deflection.

Our group of normal controls consisted of 60 employees of the Provident Mutual Life Insurance Company. The age span was fairly evenly distributed from 20 to 65 years. They had received periodic cardiovascular studies in the course of routine health examinations and were known to be in good health. Fifty-four were males and six were females. In all cases the usual six limb leads and precordial leads from V_{4R} to V_7 were made on a conventional direct writing electrocardiograph. In all individuals with horizontal hearts and in a majority of others additional leads were made in the third left intercostal space. Sufficient exploration of the chest was always performed to be sure the largest obtainable R waves were recorded from the left precordium. Then the six limb leads and the six precordial leads from V_1 to V_6 were recorded on the cathode ray oscillograph. In a few cases additional leads were made beyond the routine precordials when necessary to record the largest positive or negative precordial deflection.

The abnormal group consisted of 21 males who had a well documented episode of myocardial infarction from one to nine years ago. All had residual deep Q waves considered to be diagnostic of healed infarction in the conventional electrocardiogram. In addition to the Q waves some of the records showed notching and slurring of low frequency. The ages of the subjects by decades were 2 in the fifth, 11 in the sixth, and 5 in the seventh decades. Three were in the eighth decade, being 70, 71, and 73 years old. All were ambulatory and, except for angina pectoris in 10 individuals, they were feeling fairly well. None had any evidence of congenital, syphilitic, or rheumatic heart disease. None were in congestive failure. The heart was of normal size in 16 and slightly enlarged in 5. These five cases were also receiving digitalis. The blood pressure was within normal range in 17 and from slightly to moderately elevated in 4. The conventional electrocardiogram showed damage of the diaphragmatic wall in 11, of the anterior wall in four, and of both the anterior and diaphragmatic wall in six.

NORMAL CRITERIA

In a previous paper high frequency criteria for normal cathode ray oscillograms and examples of normal variations were presented.[1] We will summarize these briefly and bring them up to date. These criteria are not concerned with the low frequency notching and slurring which is obvious even in the conventional electrocardiogram. More than two distinct deformities consisting of either high frequency notching, slurring or marked beading, or a combination of these, was considered in excess of normal variation when these occurred in the following portions of the QRS complexes: (1) in the two-thirds of the QRS deflection farthest from the base line in the three of the six limb leads with the largest amplitude; (2) in the distal two-thirds of the R wave in deflections of the precordial leads to the left of the transitional complex.

The transitional complex as well as complexes to the right of this are frequently deformed in normal individuals. However, this is usually only slight to moderate. Therefore, marked notching, slurring or beading in such records was considered abnormal. Occasionally bizarre patterns, such as flat peaks or nadirs with or without other deformity and waviness of the QRS without definite slurring are observed. In normal individuals this is slight to moderate at most, whereas in some abnormal subjects unusually bizarre patterns of this type were observed, such as illustrated in figure 6. We have been unable to establish criteria for differentiating persons with normal hearts from those with abnormal hearts on the basis of changes in the two or three limb leads of smallest amplitude or the small component of a larger QRS deflection. However, continued studies of small deflections will not be neglected.

In our normal group there was no consistent increase in high frequency detail with advancing age. In fact, some of the most extreme normal variations have occurred in the younger individuals. We have observed no high frequency detail in the T waves so these will not be discussed and will be omitted from all but one of the illustrations to conserve space. The P waves were frequently more notched than

in the conventional electrocardiogram. Thus far we have not made any attempt to evaluate additional detail in the P waves so these will be omitted from all but one illustration.
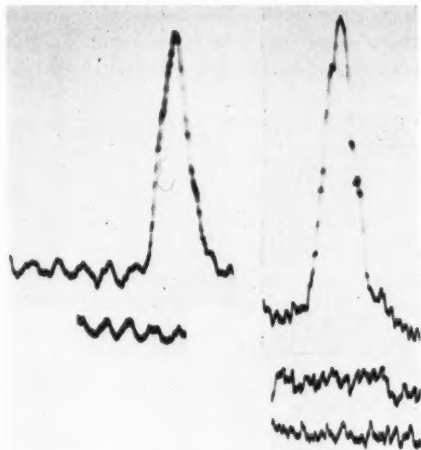

FIG. 1. The first R wave illustrates the influence of 60-cycle interference. There is a resultant moderate increase in beading. This extreme degree of 60-cycle interference was artificially induced and is never encountered normally. The second R wave shows the result of extreme induced muscle tremor. When such a degree of tremor occurs spontaneously the tracing is considered uninterpretable for high frequency detail. Additional fragments of the base line are mounted below the R waves to conserve space.

RESULTS

Of the 21 individuals with healed myocardial infarction, 14 had a degree of high frequency detail which we felt was unquestionably in excess of that observed in any of our 60 normal controls. In five individuals with healed infarction there was increased high frequency detail, but it was questionable whether it exceeded that observed in a few "extreme normals." These individuals were classified as borderline. In one of the abnormal group the interference from muscle tremor made it impossible to evaluate high frequency detail. And in one individual who had had an episode of infarction seven years before and whose tracing showed marked left axis deviation and a residual QS in lead III there was only a slight degree of high frequency detail which we would classify as within normal limits. He has been well since his acute episode and free from angina pectoris. Of the 14 individuals with excessive high frequency detail, 9 were having angina pectoris. Of the five borderline and one within normal limits only one had angina pectoris.

Leads from 10 patients were chosen to illustrate "abnormal" degrees of high frequency detail. However, let us first consider artefacts. Figure 1 illustrates the two main sources of these. The first R wave in figure 1 shows in-
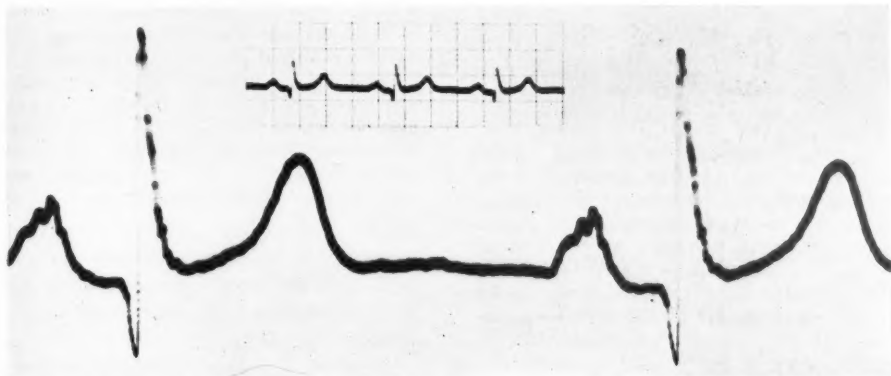
FIG. 2. This tracing was run at a much slower paper speed (130 mm. per second) than any of the others illustrated. The base line is quiet, yet there is marked beading of the R downstroke which has a consistently repetitive pattern in all R waves. This is lead II from an individual with healed diaphragmatic wall infarction. The conventional electrocardiogram mounted above the cathode ray oscillogram showed no detail in the R waves.
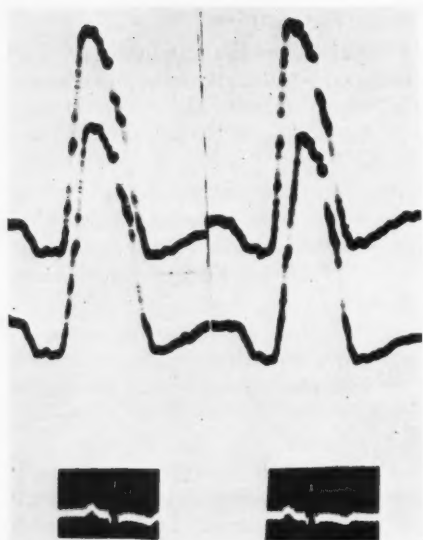
FIG. 3. This shows marked beading of the peak and early downstroke in lead II in a patient with anterior and diaphragmatic wall infarctions. This is not seen in the conventional electrocardiogram mounted below the cathode ray oscillogram. Four QRS complexes of the oscillogram are mounted to show that the beading is consistently repetitive.
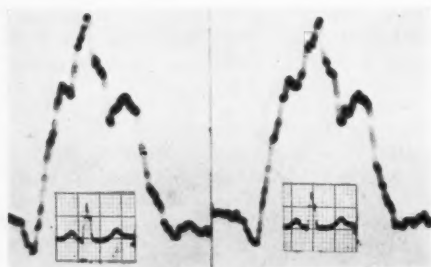
FIG. 4. Two QRS complexes illustrate marked beading of R_{II} in a subject with infarction of the diaphragmatic wall. The conventional electrocardiogram mounted below the oscillogram shows only a barely perceptible low frequency notch on the R upstroke and a slight notch on the R downstroke. All 12 cathode ray oscillograph records in this subject showed abnormal increase of the high frequency detail.

duced 60 cycle interference. In our experience the slight amount of 60 cycle interference which occasionally occurs under normal operating conditions causes no significant distortion of the QRS other than slight beading. Another

more troublesome artefact is that due to muscle tremor. The second R wave in figure shows muscle tremor induced by having the subject raise his head off the table. In the presence of marked muscle tremor high frequency detail cannot be evaluated, and even in the presence of slight to moderate irregularities of the base line due to tremor the high
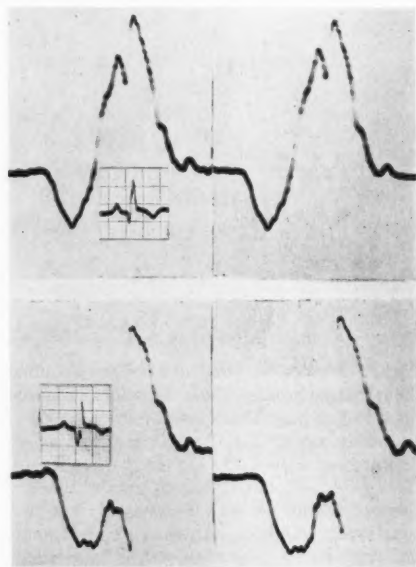
FIG. 5. The upper two complexes show marked variation in the speed of the photographic trace with excessive beading of the upper half of R_{II} in a subject with infarction of the diaphragmatic wall. The conventional electrocardiogram shows only a Q_{II} and one low frequency notch near peak of R. The lower pair of records are aV_F. In aV_F the R upstroke is so fast it fails to record in this cathode ray oscillogram. The P-QRS-T from the conventional electrocardiogram are mounted with their respective cathode ray oscillograph counterparts.

frequency detail must be interpreted with caution. Slight muscle tremor is fairly common in the limb leads but unusual in the precordial V leads.

Figures 2, 3, 4 and 5 illustrate beading which we believe is in excess of normal variation. In each instance the subject had a healed diaphragmatic wall infarction with deep Q waves in leads aV_F and III. In figure 2 the base line is quiet, yet there is marked beading which

has a consistently repetitive pattern in the R downstroke of lead II. Figure 3 shows marked beading of the peak and early R downstroke. This has been repeatedly and consistently recorded in this individual who has survived episodes of both anterior and diaphragmatic wall infarction and now has severe angina. His chest leads were also markedly deformed. For a detailed description of figures 4 and 5 the reader is referred to the legends.
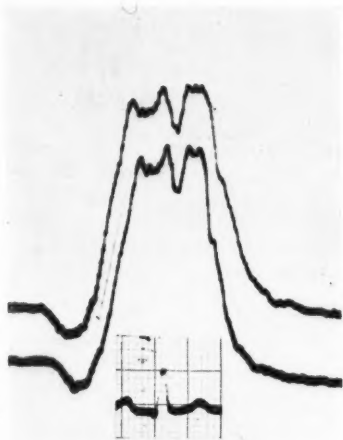
FIG. 6. This shows bizarre flattening and deformity of the top of R_{II} in a subject with infarction of the diaphragmatic wall. Two deflections of the cathode ray oscillogram are shown; one immediately below the other. The conventional electrocardiogram mounted below the oscillogram shows a slightly broad R peak.

Figure 6 shows an unusually bizarre broad peak of R_{II} in a subject with healed diaphragmatic wall infarction.

Figures 7 and 8 illustrate examples of high frequency detail definitely in excess of normal variation in individuals with anterior wall damage. In figure 7 there is excessive notching and beading in the QS in V_3 and the Qrs in V_4. In figure 8 the peaks of V_4 and V_5 are distinctly deformed. None of our 60 normals has such a distinct deformity in the peak of any predominantly positive precordial record. The diagnosis in the conventional electrocardiogram was diaphragmatic wall damage based on deep Q waves in leads II, aV_F, and III.

Yet the cathode ray oscillogram revealed abnormalities in precordial leads also.

Figure 9 illustrates serial change in V_4 after a second episode of myocardial infarction. This individual had typical Q waves in leads II, aV_F and III in June, 1951 but then the precordial leads were normal. On Sept. 19, 1951 he had another episode of myocardial infarction. One year later a cathode ray oscillogram revealed the striking serial change in V_4 illustrated in figure 9. The conventional electrocardiogram revealed normal precordial leads, whereas all the precordial leads in the oscillogram from V_4 to V_5 and at levels two inches above and below these electrode positions revealed records with deformities near
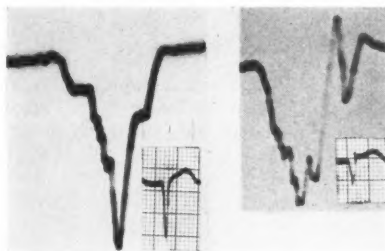
FIG. 7. This shows an abnormal increase in the high frequency detail in V_3 and V_4 of a subject with anterior wall damage. The conventional tracing reveals nothing definite in the way of notching or slurring.

the peak of R consisting of high frequency notching and beading.

In addition to the 21 individuals with diagnostic Q waves in the conventional records, four additional instances of clinically diagnosed coronary disease seem worthy of comment. We obtained a cathode ray oscillograph record without unusual high frequency detail from a 53 year old individual with angina pectoris and a history of healed myocardial infarction. His conventional electrocardiogram is also normal now but a Master two-step test had been performed and was positive. His blood pressure was 170/100 which may or may not be significant. An additional case of definite angina pectoris in an individual with both normal conventional electrocardiogram and cathode ray oscillograph record, except for

minimal S-T depression, was observed. This patient was also hypertensive, the blood pressure being 210/110. On the other hand, another patient was observed with a clear-cut episode of myocardial infarction without diagnostic

severe angina. This record is deformed far in excess of the two other records of right bundle branch block which we obtained from two healthy individuals without other history, symptoms, or signs of cardiovascular disease

FIG. 8. This shows deformities in V_3, V_4, and V_5. We have not observed this degree of deformity of the peak of V_4 and V_5 in any normal subject. The conventional electrocardiogram not mounted here revealed only the one gross low frequency notch seen in V_3.
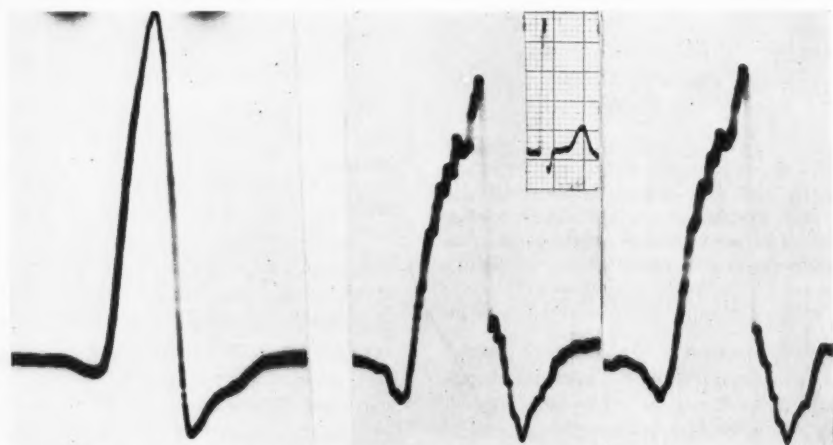
FIG. 9. The first QRS complex is lead V_4 recorded in June 1951. This deflection is perfectly smooth. The next two are successive QRS complexes from a strip of V_4 recorded in May 1953, following recovery from myocardial infarction. Marked notching is now present. The conventional electrocardiogram shows only damage of the diaphragmatic wall. See text for further details.

Q waves in the routine leads; in this patient lead II was grossly deformed in the oscillogram but not significantly so in the direct writer as illustrated in figure 10. Figure 11 illustrates a record showing right bundle branch block in a patient with healed myocardial infarction and

DISCUSSION

The purpose of this study was to determine whether individuals clinically diagnosed as having definite coronary disease had records made with a cathode ray oscillograph showing increased high frequency detail not revealed

in the conventional electrocardiogram. We felt that if this should prove to be the case, it would justify embarking upon a much larger undertaking to determine whether increased high frequency detail occurring in individuals with normal conventional electrocardiograms was of prognostic or diagnostic significance. Since this latter type of study would require observation of a fairly large number of individuals over a period of time, it seemed advisable before starting such an extensive project to examine examples of obvious cardiac disease to obtain some idea of what might be expected.
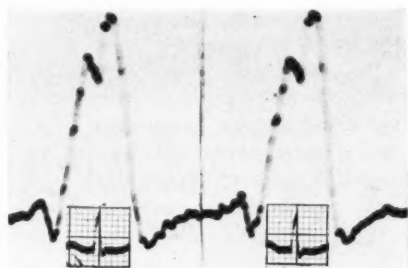
FIG. 10. This shows lead II in a subject described in the text. There is marked deformity of the peak in R_{II} whereas the conventional electrocardiogram shows only a slight slurring at the peak of the R wave.

While our experience is too limited to establish criteria for differentiation of borderline normal and abnormal records, or indeed to assert positively that there exist distinct high-fidelity criteria, we felt that, at this point, it was worth while to give a brief summary of our findings and to illustrate some of the more unusual wave forms found in individuals with coronary disease. In this latter group there is definitely increased high frequency detail, but whether its diagnostic value is worth the increased expense and time involved remains to be determined. It would have been very fortunate if all normal individuals had smooth regular records and all subjects with abnormal hearts gave records which were obviously notched or slurred. However, such a clear-cut differentiation did not always prove to be the case, so the problem of abnormal high frequency detail is quantitative as well as qualitative with some possible overlapping between

the two groups.* Criteria for the range of normal variation require further investigation. But we feel that so far in our two small series the differences have been significant in a majority of cases, and if extension of these studies continues to show the same results then the differences between the two groups may prove to be of diagnostic and/or prognostic significance.
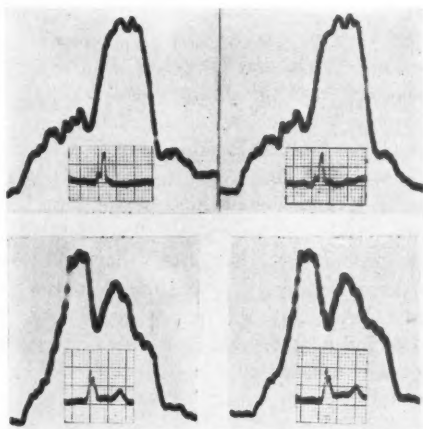
FIG. 11. This shows unusual deformity of V_2 and V_3 in a subject with right bundle branch block and longstanding coronary disease. While some deformity is also revealed in the conventional record it is much less detailed.

The increased detail in high fidelity electrocardiography, such as high frequency notching, slurring, beading and peculiar wave forms is not seen in the conventional electrocardiogram for three reasons.[2] First and foremost, is the low frequency response of the usual electrocardiograph such as the direct writer, string galvanometer, and low frequency mirror galvanometer. The second reason is the low amplification of the tracings. An amplification

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* This discussion is concerned only with differences in high frequency or other details not visible in the conventional electrocardiogram. In all 21 cases of healed myocardial infarction there were obvious diagnostic Q waves, and in some cases there was also low frequency notching and slurring, in both conventional and cathode ray records. These Q waves and other low frequency phenomena which were obviously present in the conventional electrocardiogram are not the subject of this discussion.

of such degree that 1 mv. gives a deflection of from 2 to 6 cm. may be necessary to reveal properly the high frequency detail. The third reason is the slow paper speed of the usual electrocardiograph.

The type of analysis of records used in this paper differs from the vector approach in that we have emphasized pattern detail. On the other hand, we have considered this detail significant in the limb leads only when it occurs in the three leads of largest amplitude, which of course are relatively collinear with the long axis of the QRS loop in the frontal plane. If two of the six limb leads are used for recording a loop, then all the detail found in any of the limb leads must also be present in this loop, provided it is sufficiently enlarged or magnified and is not interrupted with time signals. However, we believe this detail will be more difficult to evaluate from the loop. Furthermore, certain detail found in the precordial leads may not be present in loops recorded by distant electrodes. This problem has not been studied by us and we believe to do it adequately a "panoramic viewer"[8] employing a cathode ray oscillograph would have to be used.

In our group of 60 normal individuals there was no general tendency to increased high frequency detail with age. In fact, we found the greatest normal variation in younger people. Of course, our sample is too small to give an adequate picture.

Whatever the mechanism of the high frequency detail during depolarization, it is not appreciable during the slower processes of repolarization because we have not observed any high frequency detail in the T waves. In fact, we have observed abnormal high frequency detail in the cathode ray oscillogram of the QRS complex without any S-T or T-wave abnormalities in the conventional electrocardiogram; and on the other hand, S-T and T-wave changes in the conventional electrocardiogram may occur without high frequency detail in the QRS complex recorded by the cathode ray oscillograph.

Since we have found increased high frequency detail in cases of healed myocardial infarction, and since Zoll, Wessler and Blumgart[9] have shown that multiple myocardial infarction is the most common autopsy finding in angina pectoris, we might speculate that a majority of individuals with angina pectoris would ultimately have increased high frequency detail in tracings made with a cathode ray oscillograph. Whether this occurs frequently in the presence of a perfectly normal conventional record remains to be determined. It is possible that in some patients with early angina who have not had significant permanent heart muscle damage, there might be S-T or T wave changes with no increased high frequency detail in the electrocardiogram since the mechanism of these two phenomena would seem to be different.

Several possibilities for future studies to determine the value of this increased high frequency detail suggest themselves. The most interesting one would be to determine whether significantly increased detail occurs in the cathode ray oscillograph record of asymptomatic individuals who have normal conventional tracings, and if so, whether it is a precursor of clinically manifest coronary disease. Such a finding would be helpful in identifying coronary disease in its incipiency. Second, we have observed serial change in cathode ray oscillograms while the conventional tracing remained apparently unchanged. (See figure 9.) This could be of diagnostic value. And third, since the tracings made with the cathode ray oscillograph reveal much more detail, they might prove to be a valuable adjunct in assessing the degree of tissue damage or recovery. The great problem is to determine the time at which significant, high frequency notching, beading, and other high frequency detail begin to occur in the course of coronary disease. Do these occur before obvious low frequency abnormalities appear in the conventional electrocardiogram, or are the high frequency components later phenomena which appear concurrently with or after diagnostically significant Q waves have already made their appearance in a majority of cases? This study, which we hope to pursue, would require a long term follow-up of cases of angina and other types of individuals suspected of having coronary disease.

Summary and Conclusion

Of 21 individuals with healed myocardial infarction and residual diagnostic deep Q waves, 14 had much greater high frequency detail and bizarre patterns in their cathode ray oscillograph records than did normal individuals, 6 were borderline, and only 1 was within normal limits for high frequency detail. The possible significance of this finding is discussed. Further studies are warranted to evaluate the role of high fidelity electrocardiography in the diagnosis and prognosis of heart disease.

Acknowledgments

Sumario Español

Electrocardiografía de alta fidelidad empleando el oscilógrafo de rayo cátodo con escala de tiempo expandida, reveló identaduras de alta frequencia considerables, slurring, molduras convexas, y otras peculiaridades no vistas en trazados electrocardiográficos convencionales en los mismos individuos. Aunque algunos de los trazados de rayo cátodo contienen componentes con frequencias en exceso de 1000 ciclos por segundo, en este informe no se discutirá un analisis de la frequencia, pero en lugar los electrocardiogramas se presentaran como patrones con singular detalle que aparecerá obvio hasta al observador casual. Usando esta téncica se encontró que en 14 de 21 individuos con infartos del miocardio cicatrizados tenían una incidencia de componentes obvios de alta frequencia en los electrocardiogramas de rayo cátodo mayor que en una series de 60 controles normales. El posible significado de este hallazgo y la necesidad de más investigación se discuten.

References

[1] LANGNER, P. H., JR.: The value of high fidelity electrocardiography using the cathode ray oscillograph and an expanded time scale. Circulation **5:** 249, 1952.

[2] —: High fidelity electrocardiography: Further studies including the comparative performance of four different electrocardiographs. Am. Heart J. **45:** 683, 1953.

[3] GROEDEL, F. M.: Das elektrokardiogramm. Dresden and Leipzig, Theodore Steinkopff, 1934.

[4] REID, W. D., AND CALDWELL, S. H.: Research in electrocardiography. Ann. Int. Med. **7:** 369, 1933.

[5] GILFORD, S. R.: High fidelity electrocardiography. Proceedings of Second Joint AIEE-IRE Conference on electronics in nucleonics and medicine, New York, N. Y., October 31, 1949.

[6] DUNN, F. L., AND RAHM, W. E., JR.: Electrocardiography: Modern trends in instrumentation and visual and direct recording electrocardiography. Ann. Int. Med. **32:** 611, 1950.

[7] KERWIN, A. J.: The effect of the frequency response of electrocardiographs on the form of electrocardiograms and vectorcardiograms. Circulation **8:** 98, 1953.

[8] MILNOR, W. R., TALBOT, S. A., AND NEWMAN, E. V.: A study of the relationship between unipolar leads and spatial vectorcardiograms, using the panoramic vectorcardiograph. Circulation **7:** 545, 1953.

[9] ZOLL, P. M., WESSLER, S., AND BLUMGART, H. L.: Angina pectoris: A clinical and pathologic correlation. Am. J. Med. **11:** 331, 1951.

Some Requirements in Equipment and Technics for Vectorcardiography

By JAMES A. CRONVICH, M.S., GEORGE E. BURCH, M.D. AND J. A. ABILDSKOV, M.D.

To reduce the effects of extraneous potentials caused by muscle tremor, sweating, and interference from power circuits, it is desirable to restrict the frequency range of the cathode ray vectorcardiograph. Mathematical analysis of idealized waves and experiments with a photoelectric electrocardiographic generator indicate that a frequency range between the half-power frequency of 0.8 to 80 cycles per second is satisfactory for proper reproduction of most vectorcardiograms. Many investigators construct the vectorcardiogram graphically from the electrocardiogram. In this study it is shown that, unless simultaneous electrocardiograms recorded at greater than usual paper speed are used, such vectorcardiograms may be incorrect.

DURING the past six years the attention of cardiologists in increasing numbers has been directed toward vectorcardiography. This attention has been stimulated by the hope that this phase of electrocardiography may lead to new information of clinical importance in detecting and evaluating heart disease and of physical importance in determining the manner in which electric currents are generated by the living heart and propagated through the body.

Modern electrocardiography and vectorcardiography are intimately associated with vacuum tube amplifiers and oscillators, cathode ray oscilloscopes, and electronic timing circuits. Although the Einthoven string galvanometer is satisfactory for electrocardiography, modern automatic vectorcardiography would be impossible without the vacuum tube amplifier and the cathode ray oscilloscope. Theoretically the combination of vacuum tube amplifiers and cathode ray tubes should constitute the perfect vectorcardiograph. With this system the amplifier alone is the limiting factor in both low- and high-frequency reproduction. With a suitable direct-coupled amplifier all of the frequencies encountered in vectorcardiography may be reproduced properly. In practice, however, a drift-free, wide-band,

direct-coupled amplifier having the required voltage gain of approximately 200,000 is difficult to construct and maintain. Moreover, the effects of extraneous voltages due to sweating at the electrode sites, both low- and high-frequency skeletal muscle activity, respiration, changes in the position of the subject, and inductive and electrostatic interference from adjacent power circuits and electrical equipment make it advisable to restrict as much as possible both the low- and high-frequency limits of the vectorcardiograph.

A theoretic study was made to determine the approximate frequency requirements for a satisfactory vectorcardiograph. In addition, a photoelectric generator was constructed which could produce voltages similar in waveform to those encountered in vectorcardiography. With the generator, it was possible to demonstrate some of the errors which may occur when the vectorcardiogram is constructed graphically from standard electrocardiograms, and to determine by means of frequency attenuating networks the influence of the frequency response of the vectorcardiograph.

THEORETIC ANALYSIS

In order to make a reasonably simple approach to a theoretic determination of the frequency requirements in vectorcardiography, assumptions were made regarding the duration and configuration of the waveforms likely to be encountered and the circuits used. The QRS complex is the shortest component with a minimum duration of about 0.04 second and the T wave is the longest with a maximum du-

ration of about 0.5 second. Intervals outside this range may be encountered in special circumstances but are unusual and were not considered in this analysis.

Usually, the duration of the QRS complex is about 0.08 second and of the T wave about 0.15 second. The QRS complex was considered to be a triangular pulse with equal rates of rise and fall, and the T wave either a triangular pulse or a half-wave sine pulse.

Since the voltage amplification required in vectorcardiography with the cathode ray tube is approximately 200,000 times, a maximum of three stages of amplification is necessary. Without serious difficulty due to drift, two of the stages can be direct-coupled so that only one R-C coupling network, which affects the low-frequency response, is necessary between stages. Therefore, only the single R-C coupling network shown in figure 1a was studied in detail to determine its effect on the relatively low-frequency T wave and loop.

Likewise, to restrict the high-frequency range, shunt capacitance would ordinarily be used in only one stage. The single R-C network shown in figure 1c was studied in detail to determine its effect on the relatively high-frequency wave and loop of the QRS complex. Because the ratio of the duration of the longest T wave to that of the shortest QRS complex likely to be encountered is over 12:1, it was assumed that in a practical vectorcardiograph the effect of the R-C coupling networks on the low-frequency response should be relatively unaffected by the shunt capacitance which limits the high-frequency response, and vice versa.

The pulses considered in this analysis are shown in figures 1e and 1f. The method of the Laplace transform was used to analyze the response of the various networks. Although the double networks of figures 1c and 1d were considered, they were not studied in detail. After the effect of the network on the time variation of the pulse was calculated, Lissajous patterns combining two of the input waves and two of the output waves could be drawn and compared for various phases between input components.

THE PHOTOELECTRIC GENERATOR

A photoelectric generator for producing artificial electrocardiographic potential differences was built to evaluate both the possible errors in methods of graphically constructing the vectorcardiogram and the effect on the vectorcardiogram of the frequency characteristics of the recorder. With this unit, changes in the relative phase between "electrocardiographic" leads could be made readily and a study could be carried on without the difficulties involved in trying to obtain reproducible sequential records from a human subject. The basic circuit of the generator and its con-
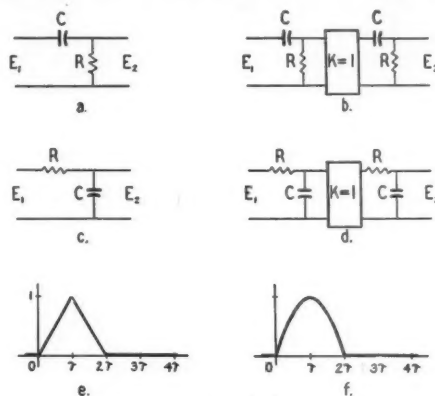
FIG. 1.   Frequency-attenuating networks and pulses considered in the theoretic analysis. (*a* and *b*) Low-frequency attenuating networks. (*c* and *d*) High-frequency attenuating networks. (*e*) Triangular pulse. (*f*) Half-wave sine pulse.

nections to a cathode-ray oscilloscope for these studies is shown in figure 2.

The generator consisted of a 6-watt fluorescent lamp as a light source, a lucite tube which was masked with tape to produce light variations resulting in patterns corresponding to desired electrocardiograms and driven by a phonograph motor at 78 revolutions per minute, two photoelectric cells, two cathode-follower amplifiers, and suitable rectifier and filter circuits. The output impedance of the cathode followers was approximately 2500 ohms. The cathode-ray oscilloscope employed direct-coupled amplifiers with essentially flat response to 100,000 cycles per second. Consequently, all of the important frequency modification could

be obtained in the networks which were inserted between the cathode followers and the input terminals of the oscilloscope.

The fluorescent lamp was inserted along the axis of the lucite tube and was supplied with rectified and filtered current to avoid variations in light intensity which would result from operation with alternating current. To start it, one of its filaments was heated through a series resistor and the lamp was short-circuited. The inductive surge from the filter inductor on removal of the short-circuit started the lamp satisfactorily, and then the filament-heating circuit was opened. The photocells could be moved forward or backward in the direction of rotation to advance or delay one "electro-

$CR = 4$ seconds and $2\tau/CR = 0.125$, there is for the 0.5-second triangular wave a 3 per cent reduction of peak amplitude and 6 per cent overshoot on return to zero, and a premature return to zero of 0.025 second. Reduction of CR causes proportional increases of all of these effects. Inspection of the T wave of the experimentally obtained electrocardiograms of figures 4 and 5 shows how these distortions increased as CR was reduced. However, for a given ratio $2\tau/CR$, the experimental distortion was about one-half of that predicted by the analysis. The effect of low-frequency attenuation on the reproduction of the T and P loops of the vectorcardiogram is shown in figure 6. The overshoot artefact
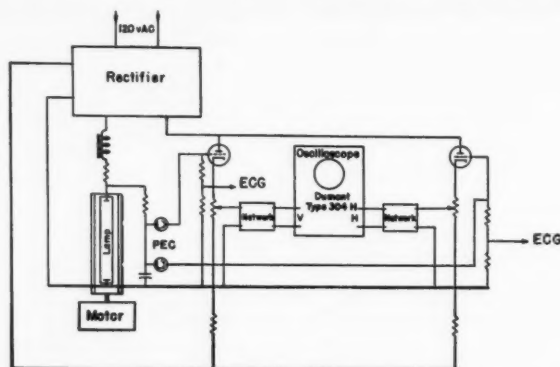
FIG. 2. Basic circuit of photoelectric generator showing connections to frequency-attenuating networks, oscilloscope, and string galvanometer electrocardiographs.

cardiogram" with respect to the other. It was also possible to record simultaneously the "electrocardiograms" with two string galvanometers of the type employed in electrocardiography connected, as shown in the diagram, from the terminals ECG to ground.

RESULTS

Some of the results of the theoretic analysis and of the experimental tests with the photoelectric generator are shown in figures 3 through 10. The analysis shows that the important effects of limiting the low-frequency response are reduction of peak amplitude of the reproduced wave, overshoot on the return to zero, and premature return to zero. As shown in figure 3 when the time constant of the network
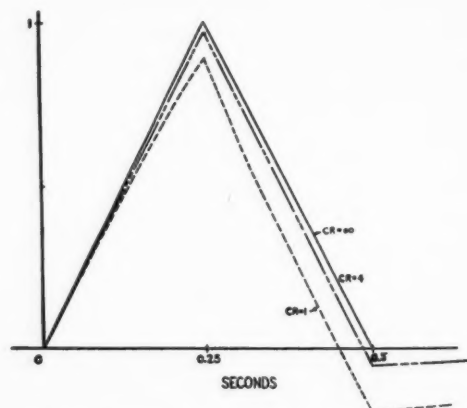
FIG. 3. Theoretic response of single low-frequency attenuating networks to triangular pulse representative of the T wave.

when CR = 0.4 second is evident and is pre-
dicted by space-quadrature combination of
the modified triangular pulses of the theoretic
analysis. Analysis with the sine pulse agreed
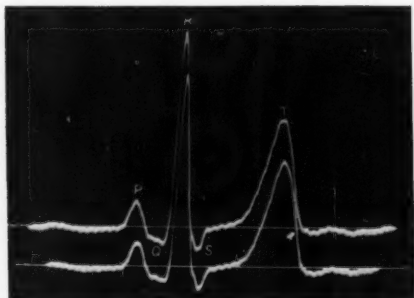closely with that for the triangular pulse.

FIG. 4. Experimental response of single low-fre-
quency attenuating network to generated electro-
cardiogram. Duration of T wave $2\tau = 0.14$ second.
Upper trace with direct-coupled circuit (CR = ∞;
$2\tau/CR = 0$ for the T wave). Lower trace with R-C
coupling network (CR = 2 seconds, $2\tau/CR = 0.07$).
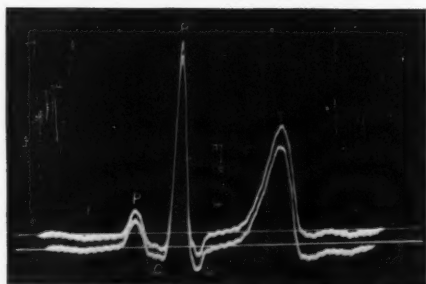
FIG. 5. Experimental response of single low-fre-
quency attenuating network to generated electro-
cardiogram. Upper trace with direct-coupled circuit.
Lower trace with R-C coupling network (CR = 0.4
second; $2\tau/CR = 0.35$ for the T wave).

Limitation of the high-frequency response
is most evident in reproduction of the QRS
complex. Analytically the effects were delay
and reduction of the peak amplitude of the
reproduced pulse. As shown in figure 7, the
network with CR = 0.002 second reduced the
peak of the 0.04-second triangular pulse by 6
per cent and delayed the pulse by 0.002 second.
In this case $2\tau/CR = 20$. The peak reduction
is approximately proportional to CR and con-
stant for a given ratio $2\tau/CR$. The delay, es-

sentially independent of the pulse duration, is
equal to the time constant of the network.
The peak reduction of the steep component of
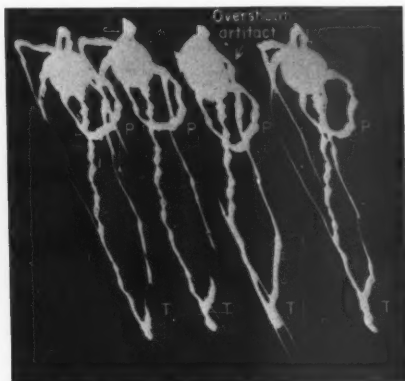
FIG. 6. Experimental effect of single low-frequency
attenuating network on the generated vectorcardio-
gram. Circuit conditions reading from left to right
were as follows for horizontal and vertical circuits of
the oscilloscope: direct-coupled; R-C coupled, CR =
2 seconds; R-C coupled, CR = 0.4 second; R-C
coupled, CR = 2 seconds for vertical circuit, CR =
0.2 second for horizontal circuit. Only part of QRS
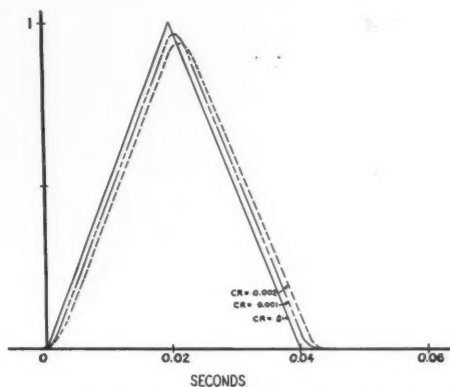loop shown. Dissimilar waves in horizontal and
vertical circuits.

FIG. 7. Theoretic response of single high frequency
attenuating network to triangular pulse representa-
tive of the QRS complex.

the experimentally produced electrocardiogram
is shown in figure 8. Satisfactory agreement
between theory and experiment was indicated
by an experimental peak reduction of about 5
per cent when $2\tau/CR = 27$. The shortening of

the major axis of the QRS loop as a consequence of high-frequency attenuation, with little change in its direction or in the configuration of the loop, is shown in figure 9.
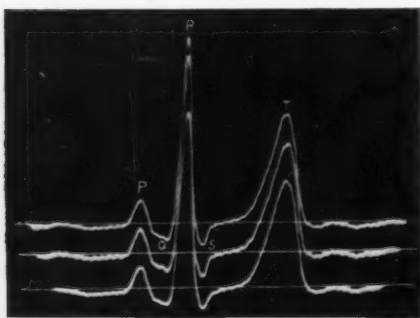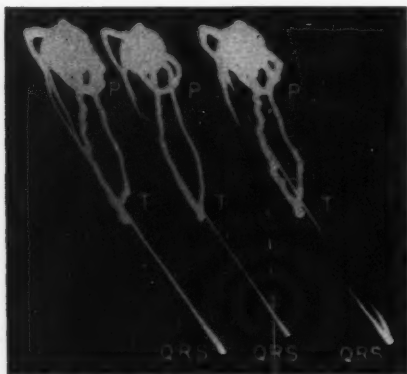

Fig. 8. Experimental response of single high-frequency attenuating network to generated electrocardiogram. Duration of steepest segment of QRS complex $2r = 0.08$ second. Top trace with R-C network (CR = 0.003 second; $2r/CR = 27$ for segment of QRS complex). Middle trace with direct-coupled circuit (CR = 0; $2r/CR = \infty$). Bottom trace with R-C network (CR = 0.005 second; $2r/CR = 16$).

Fig. 9. Experimental effect of high-frequency attenuating networks on the generated vectorcardiogram. Circuit conditions, reading from left to right, were as follows: direct-coupled; R-C networks, CR = 0.003 second; R-C networks, CR = 0.001 second in vertical circuit; CR = 0.0005 second in horizontal circuit.

The effect of different time constants in the circuits to the vertical and horizontal amplifiers is shown in the right-hand vectorcardiograms of figures 6 and 9. This narrowing or widening of the loops is to be expected because of the

difference in phase shift of the vertical and horizontal electrocardiographic waves as a result of the difference in time constants.

Of importance to many experimenters who graphically construct the vectorcardiogram are the effects produced by changes in the relative time-phase of the horizontal (I) and vertical components (VF) of the vectorcardiogram. These effects are shown in figure 10. The three vectorcardiograms are obviously different, yet they were produced by the same electrocardiographic patterns which, in their correct relative time-phases, are shown below the corresponding vectorcardiogram. The differ-
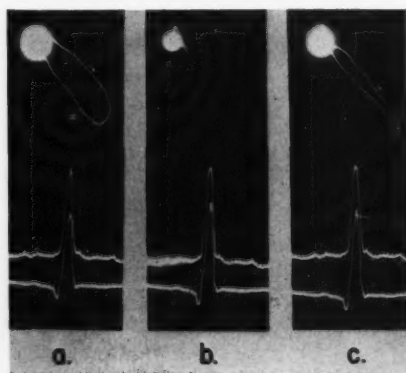

Fig. 10. Effect of changes in time-phase between horizontal and vertical components of a generated vectorcardiogram. (a) Lead I advanced 0.004 second; (b) reference; (c) lead I retarded 0.004 second. Duration of complex = 0.09 second.

ences in the vectorcardiograms are the result of almost imperceptible differences in the relative time-phases of the electrocardiograms. If we consider the middle group as the reference with the vectorcardiograms traced clockwise, that on the left with the vectorcardiogram traced clockwise was obtained by advancing lead I by 0.004 second, and that on the right with the vectorcardiogram traced counterclockwise but more open than the reference was obtained by retarding lead I by 0.004 second. Such small differences in time phase are imperceptible in simultaneously recorded electrocardiograms even with the paper speed double the usual value. They are certainly imperceptible in these electrocardiograms which

were recorded on a cathode ray tube. If such differences can be obtained with simultaneously recorded electrocardiograms, the possible errors introduced by attempting to construct the vectorcardiogram from leads which may have been recorded some minutes apart can be realized. All of the variations produced by changes in heart rate, position of the subject, respiration, etc., superimpose their effects on the graphically constructed vectorcardiogram. Although some of the errors can be avoided by using all three standard lead electrocardiograms in the construction and constantly checking to see that leads I + III = lead II, the difficulty is considerable and the results of graphic construction are questionable.

Conclusions

Considering the results of both analysis and experiment, it would seem that reproduction of the vectorcardiogram with accuracy within the limits imposed by normal biologic variations can be obtained if the time-constant of the single R-C coupling network in the amplifiers is approximately 2 and if the time constant of the single R-C network to produce high-frequency attenuation is 0.002. These correspond to a lower half-power frequency of approximately 0.08 cycle per second and to an upper half-power frequency of approximately 80 cycles per second. For many cases, smaller bandwidth than this would be satisfactory. However, some studies of high-frequency phenomena associated with electrical activity of the heart may require a higher upper half-power frequency.

It is important that all amplifiers used to reproduce the vectorcardiogram have almost identical frequency characteristics if the undesirable effects of unequal phase shifts are to be avoided.

The fact that satisfactory reproduction of the higher frequency components can be obtained with an upper half-power frequency of 80 cycles per second means that it may be possible to construct a direct-writing vectorcardiograph and thus avoid the requirement of photographic processing. It should be

emphasized that the equipment requirements considered in this study are based on those components of the electrocardiograms whose variations are known to have clinical significance. It is entirely possible, for example, that higher frequency components of the electrocardiogram may be assigned clinical importance in the future in which case the equipment requirements outlined may not be satisfactory.

Unless extreme care is exercised in the construction of the vectorcardiogram by graphic means, errors are possible in both the configuration of the loops and the direction in which they are traced. The careful use of simultaneously recorded, standard-lead electrocardiograms avoids some of these difficulties. However, there is considerable question regarding the accuracy obtained when sequential records are employed, because of the difficulty of determining corresponding points in waves which may be recorded at different heart rates, with different phases of respiration, and with different conditions of muscular activity.

Sumario Español

Para reducir los efectos de potenciales extraños causados por temblor muscular, perspiración e interferencia de circuitos eléctricos, es deseable restringir el alcance de la frecuencia del vectorcardiógrafo de rayo cátodo. Analisis matemático de ondas ideales y experimentos con un generador electrocardiográfico fotoeléctrico indican que el alcance de la frecuencia entre la medio frecuencia de 0.8 a 80 ciclos por segundo es satisfactoria para la propia reproducción de la mayoría de los vectorcardiogramas. Muchos investigadores construyen el vectorcardiograma gráficamente del electrocardiograma. En este estudio se demuestra que, amenos que los electrocardiogramas no sean registrados simultáneamente a velocidad del papel mayor que lo usual, estos vectorcardiogramas pueden ser incorrectos.

REFERENCE

Gardner, M. F., and Barnes, J. L.: Transients in Linear Systems. New York, John Wiley & Sons, 1942.

The Normal Electrocardiogram

By CHARLES E. KOSSMANN, M.D.

ONE of the most difficult tasks which confronts the worker in the life sciences is to define a normal. The difficulty is compounded when the measurement to be made is affected by many variables which differ in importance from time to time. These remarks apply to the electrocardiographer, and to the normal electrocardiogram.

Some variables which affect the electrocardiogram are quite well known. They include phase of respiration, heart rate, recent ingestion of food, position and age of the subject. Equalization of the first four is usually achieved by recording the curve during quiet respiration with the subject in a basal state, usually recumbent; effects of age are solved by devising norms for different age groups.

Other variables are less well known. Technical errors of various kinds must be guarded against. One of these, excessive electrode jelly which makes contact with jelly at adjacent points, has been shown[1] to cause considerable distortion of deflections of precordial leads, particularly inversion of the T waves farther to the left than is actually the case. The possibility of distortion of the electrocardiogram by the recording device is usually ignored. The electrocardiogram is made up of a series of transients and intervals. The fidelity with which these are reproduced will depend on the frequency characteristics and the timing accuracy of the instrument used. Despite this basic physical tenet, it is rare to see a paper on

electrocardiography in which a frequency response curve of the instrument is included, or in which the accuracy of the timing device has been frequently tested. The clinical investigator usually accepts the manufacturer's claims for the instrument without actual test or check.

Other difficulties enter the problem. One of these is the statistician's "error of measurement" by which is meant that two different people measuring the same interval may get a different result. More important are the different definitions of a similarly designated interval or deflection by different workers. It is not certain but possible that older data on the normal electrocardiogram cannot be used for a precise study because the gradual change in the habitus of Americans, at least, makes it likely that the normal electrocardiogram of today is somewhat different than it was 40 years ago. Along this same line of reasoning, consideration must be given to racial and sex differences. Lastly, as new leads are used, new criteria for their interpretation must be established from time to time as knowledge of their normal variations accumulates.

There is one other consideration. A continuous distinction must be made between the normal electrocardiogram and the normal heart. If this is not done it becomes exceedingly difficult to define the limits of the normal record. By carefully observing this distinction, a definition of the normal electrocardiogram reduces to giving values for intervals and deflections usually found in normal subjects in various age groups. To go further would be to go beyond the electrophysiologic aspects of cardiac function, and hence to define instead the normal heart. Where this is unavoidable, as under rate and rhythm, defining the normal reduces itself largely to a simple and to some

xtent arbitrary standardization of nomencla-
ure.

With so many aspects of the problem to
bedevil him, it is small wonder that the clini-
cian, with a few notable exceptions, has made
no comprehensive, statistically mature effort
to define the normal electrocardiogram. A
further deterrent to such an effort has been the
introduction of a means of synthesizing the
QRS and T deflections of the conventional
leads into two spatial vectors with angular
relations to each other.[2] The simplification
achieved is of considerable use but tends to
obscure the less pronounced diagnostic ab-
normalities which are seen in the conventional
leads. Further, to use the method, conventional
leads must be recorded in the first place.

The need for normal values of various elec-
trocardiographic deflections and intervals has
not passed. The present communication cannot
be regarded as the desired ultimate effort to
meet this need but rather as a progress survey
which may be immediately useful. With more
time for the intensive use of statistical technics[3]
it probably can be developed at a later writing
into a more detailed and exact approach to the
truth as it applies to the normal electrocardio-
gram.

Rate and Rhythm

For the purposes of standardizing electro-
cardiographic nomenclature, it has been
generally agreed to designate a heart rate of
60 to 100 beats per minute as *normal sinus
rhythm* provided the pacemaker is in the
sinoatrial node. Any rate below 60 per minute
from the same pacemaker is designated as
sinus bradycardia; a rate above 100 per minute
is called *sinus tachycarida*.[4] These limits and
terminologies are used principally for con-
venience and for uniformity of designation.
They do not define normality except in a
gross way. Actually the normal heart rate in
young adult subjects may vary from 38 to 110
beats per minute.[5] In infants and children the
rates may vary from 55 to 205 beats per
minute.[6]

To define a normal rhythm is a rather diffi-
cult procedure. In most instances of sinoatrial
rhythms there are slight variations in cycle
lengths. Arbitrarily when these vary by more
than 10 per cent in length in any given strip of
electrocardiogram, the record is said to display
sinus arrhythmia. A great variety of dysrhyth-
mias may occur in the normal subject,[5] but
in the normal electrocardiogram the four
rhythms defined are encountered most often.

Intervals

The P-R Interval

One of the important aspects of establishing
normal limits for the P-R interval is to stand-
ardize the method of measuring it. There is
general agreement that it should be measured
from the beginning of the P wave to the very
first evidence of ventricular excitation whether
this be the beginning of Q, QS, or R. Unfor-
tunately agreement does not exist on which
lead gives the most nearly correct P-R interval.
In certain leads the beginning of QRS may be
obscured if these leads are so oriented with
respect to the early electromotive forces coming
from the ventricles as to show no deflection.
This will result in a falsely long P-R interval.
On the other hand, if a lead records the be-
ginning of the P wave poorly, the P-R interval
will be falsely abbreviated. In the bipolar leads
the closest approximation to the true P-R
interval can be made by taking the difference
between the longest QRS interval in leads I,
II, and III and the longest P-S interval (be-
ginning of P to the end of QRS) in these leads.[7]
This difference will be the same as the longest
P-R interval in these leads in 97.4 per cent of
electrocardiograms of patients. Since it is easier
to measure the longest interval, this has come
to be the standard despite the known error
in some instances. If simultaneous leads are
available the interval is most accurately given
by the distance from the beginning of the earli-
est P wave to the beginning of the earliest
QRS.

The P-R interval is known to lengthen with
age and shorten with rapid rate, although there
is a difference of opinion regarding the latter.[8, 9]
On the basis of these supposed relationships
elaborate tables have been constructed, but
for usual clinical purposes more general and
easily usable definitions can be given. In the bi-
polar and unipolar extremity leads with normal

heart rates, its upper limit of normal in adults is 0.20 second; in adolescents, ages 14 to 17 years, 0.18 second; and in children under 14 years of age, 0.16 second. In precordial leads of children its maximum duration may be the same, shorter, or longer,[6] and differences if present may be as much as 0.04 second. Extensive measurements of the atrioventricular conduction time in precordial leads do not seem to have been made in adults. It is for this reason that the maximum normal values given apply only to the bipolar and unipolar extremity leads.

The lower limit of normal is usually stated to be 0.12 second, but exceptions are not infrequent. A precise definition of the lower limit must await more precise statistical study.

The greatest disagreement found in the literature is with the maximum normal P-R interval of 0.20 second in adults. Many feel it should be longer, and the figures of 0.21 or 0.22 are often given. Actually, only a small percentage of normal subjects will show a P-R interval in excess of 0.20 second[8]; the great majority of records exceeding this value will be of patients with heart disease. When the measurement is borderline, a recheck, with the points made above in mind, is desirable. A final opinion of its significance will naturally depend on associated clinical and laboratory data.

The QRS Interval

There is no problem with regard to measuring the QRS interval. The widest one found in any lead is correct. Since detailed data are not available on its duration in precordial leads it is customary to measure it in the bipolar or unipolar extremity leads.

The QRS interval varies in duration directly with age and inversely with heart rate. The changes which occur with rate are quite small and probably do not exceed 0.007 second for a rate change as large as 60 beats per minute.[10] The changes with age are significant and make it necessary to construct standards for different age groups.

The maximum normal QRS is 0.10 second in adults, 0.09 second in children from 5 to 14 years old, and 0.08 second in children under

5 years old. In the precordial leads these values may be larger; in children the excess may occasionally be as much as 0.03 second.[6]

Most disagreement is found in the literature with the maximum normal value of 0.10 second given for adults. It is claimed that in a normal subject the QRS interval may be 0.11 or 0.12 second. This is true but it involves the problem alluded to earlier, namely the failure to distinguish the normal electrocardiogram and the normal heart. Possibly 3 per cent of normal subjects will show a QRS interval in excess of 0.10 second but most often an interval beyond this duration will be associated with disease of the heart.

There is no lower limit of the QRS interval usually given though it practically never is less than 0.06 second in adults, or 0.04 second in newborn children.

The Q-T Interval

Difficulties in measurement of the interval between the beginning of QRS and the end of the T wave arise from four principal sources: the U wave, superimposition of P and T waves, bundle-branch block, and ventricular arrhythmia.[11, 12] The U wave tends to appear as part of the T wave in certain leads. Accurate differentiation can usually be made by simultaneous recording of a lead, usually from the precordium, in which the U wave is sharply demarcated from the T wave. Bundle-branch block will prolong the Q-T interval by an amount equal approximately to lengthening of QRS alone. By correcting the Q-T interval for this difference from a prediction of what the normal QRS interval should be for the age and heart rate of the subject concerned, a rough approximation of the Q-T interval can be made.[13] With rapid rates or prolonged P-R interval, the P wave will be superimposed on the preceding T wave. The difficulty can at times be resolved with simultaneous leads as described for the U wave. Variations in ventricular rate, as with premature systoles or atrial fibrillation, require the measurement of several Q-T intervals and determination of the average in order to approach the true value. Taran and Szilagyi[11] have shown that at least 36 seconds of continuous record must be measured for a precise result if there

i- sinus arrhythmia. If only three successive cycles are measured the error is ± 12.5 per cent but can be reduced to ± 5 per cent by measuring 12 successive intervals. With a normal sinus rhythm the error of measurement when using only three successive cycles will be ± 4.5 per cent.

The longest Q-T interval is the most nearly correct, although it may be falsely prolonged if care is not taken to distinguish the U wave from the T wave. The lead to be used is the one in which the Q-T interval is clearly de-

known as the corrected (for rate) Q-T interval, or $Q\text{-}T_c$.

It must be apparent from the difficulties in measurement alluded to above that a routinely determined $Q\text{-}T_c$ of necessity must be a rather gross procedure. If the error of measurement, for example, is at least 5 per cent to 12.5 per cent even if 3 to 12 cycles are measured when there is a sinus arrhythmia, there can be little point in attempting to define differential values down to the third place depending on age or sex of the subject. Without going into all the

TABLE 1.—*Q-T Interval Corrected for Rate* $(Q\text{-}T/\sqrt{\text{R-R}})$ *as Observed in Different Normal Series*

Author	No. Subjects	Sex	Age	$Q\text{-}T_c = Q\text{-}T/\sqrt{\text{R-R}}$					
				Min.	Max.	Mean ($\bar{x}$)	Stand. Dev. (S_x)	Range ($\bar{x} \pm 2S_x$)	Range ($\bar{x} \pm 3S_x$)
Bazett,[14] 1918	15	M	14 to 40	0.342	0.392	0.368	—	—	—
	19	F	20 to 53	0.356	0.444	0.399	—	—	—
White, Kossmann, Ershler,[16] 1942	17	M	18 to 25 (approx.)	0.326	0.397	0.3676	0.0198	0.3280 to 0.4072	0.3082 to 0.4270
Cheer and Li,[18] 1930	75	M	14 to 47	0.343	0.403	0.3741	0.0135	0.3471 to 0.4011	0.3336 to 0.4146
	41	F	18 to 36	0.354	0.413	0.3880	0.0158	0.3564 to 0.4196	0.3406 to 0.4354
Stewart and Manning,[17] 1944	500	M	18 to 32	—	—	0.38	0.03	0.32 to 0.44	0.29 to 0.47
Graybiel, McFarland, Gates, Webster,[5] 1944	1000	M	20 to 30 ($\bar{x}$ 23.7)	0.30	0.59	0.383		—	—

marcated and may be an extremity lead or a precordial lead.

There is a well-known inverse relationship between the Q-T interval and the heart rate. A variety of formulas are available for predicting what the Q-T interval should be with any given rate. In the usual range of heart rates, all of these formulas make rather similar predictions. It is at the extremes of rates where differences are most evident.

One of the simplest and most universally used is Bazett's Index,[14] usually expressed as a ratio of the Q-T interval to the square root of the cycle length. This ratio has come to be

data available,[14-18] some of which is summarized in table 1, it is probably sufficiently close to the truth to define the maximum normal $Q\text{-}T_c$ for any age or sex as 0.425. A value above 0.425 should be described as a "prolonged $Q\text{-}T_c$" but may not necessarily be abnormal.

Q-R Interval (Time of the Intrinsicoid or RS Deflection)

The intrinsicoid or RS deflection ordinarily begins at the peak of R and ends with the nadir of S. It is usually the steepest and largest downstroke of QRS in the unipolar leads. In the "transitional zone" and sometimes in leads

from the right side of the precordium there may be two R waves. This sometimes is called a double intrinsicoid deflection, but the largest downstroke is usually accepted as the characteristic one for that lead. Sometimes in the midprecordium the principal downstrokes, if two are present, will vary in size with forced respiratory effort ascribed to movement of the heart and altered orientation of its ventricular surfaces to the fixed precordial electrode.

In direct leads and probably in semidirect leads from the precordium the peak of the R wave represents the beginning of excitation of

A variety of ways are available for measuring it, the most exact probably being the comparison of intervals on either side of the precordium after referral of each to a fixed point in a simultaneously recorded lead.[20] This is not often clinically expedient so that absolute values have been established for the time in each lead between the beginning of QRS and the peak of the R wave (Q-R interval). In the case of leads V_1 and V_2 the maximum normal usually accepted is 0.03 second; for leads V_5 and V_6, 0.05 second.[21, 22] If there is no R wave it is clear that the interval is zero. The actual
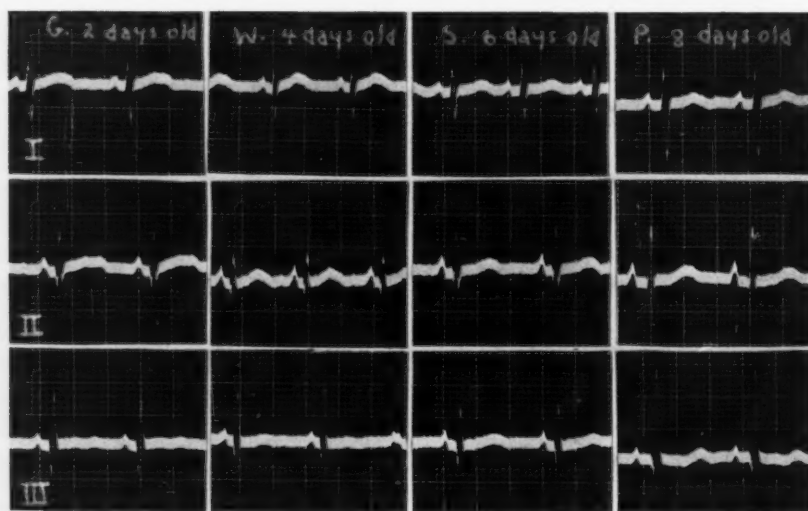

Fig. 1. Bipolar extremity leads (I, II, III) of four newborn infants showing the right axis deviation of QRS at this stage of life. Patients G. and S. were female; patients W. and P. were male. Time lines, 0.04 second.

the underlying myocardium. The completion of this process is represented by the end of the RS deflection or nadir of the S wave. A measurement of the time of the latter would probably be an exact measure of the completion of depolarization of the subjacent myocardium if it were not for the fact that this deflection is so often deformed by simultaneous electrical events occurring elsewhere in the ventricular muscle.[19] This is not so common in the case of the R wave, and clinically the time of this deflection is the one taken as indicating in a relatively gross way the arrival of excitation at the epicardial surface of the nearby myocardium.

values observed in two different groups of normals measured with a comparator are shown in table 2.

DEFLECTIONS

Absolute Size

The measurement of deflections, to be comparable, must be made in a standard way with a standard reference level. The need for such standardization was met with publication some years ago[23] of the recommendation that the reference level for the P wave, the T_P wave, the S-T segment, the T wave, and the U wave be the T-P or U-P interval. All other deflections, Q, R, S, and S-T junction (or J),

TABLE 2.—*Measurement in Seconds of Precordial Electrocardiographic Intrinsicoid (RS) Deflections in Normal Subjects Made with a Comparator. In the Series of 30 the Point of Reference Was the Beginning of QRS in Lead I; in the Series of 100 It Was the Beginning of QRS in the Same Precordial Lead as the Measured Intrinsicoid Deflection*

Reference	Subjects			Lead	Min.	Max.	Mean $(\bar{X})$	Stand. Dev. (S_x)	Range	
	No.	Sex	Age						$\bar{X} \pm 2S_x$ (95%)	$\bar{X} \pm 3S_x$ (99.7%)
Kossmann and Johnston,[20] 1935	30	M	20 to 35	V_1	0.006	0.033	0.0172	0.0064	0.0044 to 0.0300	−0.0020 to 0.0364
				V_2	0.003	0.039	0.0193	0.0085	0.0023 to 0.0363	−0.0062 to 0.0448
				V_3	0.013	0.049	0.0314	0.0097	0.0120 to 0.0508	0.0023 to 0.0605
				V_4	0.023	0.055	0.0349	0.0075	0.0199 to 0.0499	0.0124 to 0.0594
				V_5	0.023	0.053	0.0336	0.0074	0.0188 to 0.0484	0.0114 to 0.0558
Sodi Pallares, Parás, Carbrera Costío, and Mendoza,[21] 1946	100	M	10 to 20	V_1	0.000	0.031	0.020	0.0043	0.0114 to 0.0286	0.0071 to 0.0329
				V_2	0.012	0.030	0.022	0.0039	0.0142 to 0.0298	0.0103 to 0.0337
				V_3	0.014	0.044	0.026	0.0050	0.0160 to 0.0360	0.0110 to 0.0410
				V_4	0.015	0.052	0.029	0.0061	0.0168 to 0.0412	0.0107 to 0.0473
				V_5	0.022	0.053	0.037	0.0066	0.0238 to 0.0502	0.0172 to 0.0568
				V_6	0.024	0.050	0.037	0.0063	0.0244 to 0.0496	0.0181 to 0.0559

are to be measured from the P-R segment as a reference level. The reason, clearly, is that this latter segment may be displaced by an electromotive force generated during atrial recovery to create a new baseline for all deflections written during the displacement. The exact termination of this displacement cannot be determined and undoubtedly varies. Somewhat arbitrarily, therefore, the cutoff has been taken as the S-T junction, with the S-T segment just beyond it being referred rather to the T-P segment.

Newer data on the size of electrocardiographic deflections measured in the recommended way and presented in a form suitable for simple statistical arrangement is not extensive. The publications used in the construction of tables 4 to 7 are shown in table 3.[3, 6, 20, 22, 24-30] These were selected from a considerably larger number because the information they contained was adjudged to have been collected and analyzed in a relatively uniform manner. But inspection of the table will show that even after selection, there are differences which theoretically could give widely varying results. The 11 groups of investigators used six different types of instruments; the varied groups studied included Americans, Mexicans, and Brazilians; and even the technic of recording the unipolar extremity leads varied a little. The pooled results are given in tables 4 to 7, but if the reader desires more specific data, table 3 is included to help him locate it.
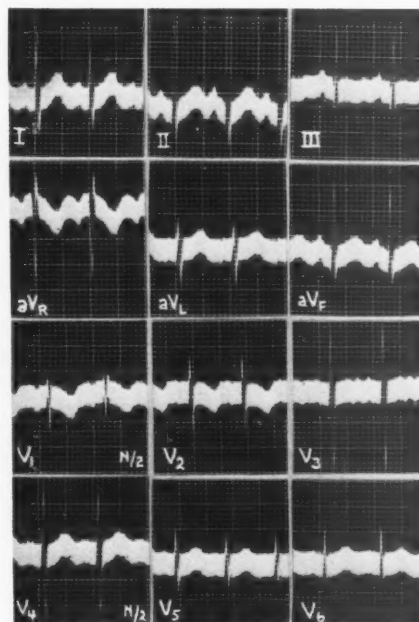

FIG. 2. Normal white male child, age 9 months. Illustrated are the bipolar extremity leads (I, II, III), the augmented unipolar extremity leads (aV_R, aV_L, aV_F), and the unipolar precordial leads (V_1 to V_6). The last were made with the string sensitivity half of normal (1 mv = 0.5 cm.). Time lines, 0.04 second. To be noted especially is the variable R′ in lead V_1, the inverted T waves in leads V_1 and V_2, and the notched T wave in lead V_3.

The problem of dividing the data according to age groups arose. The decision made for this presentation is shown in tables 4 to 7 in which

TABLE 4.*—*Normal Children, Newborn to 1 Year Old, Supine. Size of the Electrocardiographic Deflections in the Bipolar Extremity, Augmented Unipolar Extremity, and Unipolar Precordial Leads Is Given in Tenths of a Millivolt*

Lead	P				Q				R				S				RS				S-T				T			
	No. Cases	Min.	Max.	Mean	No. Cases	Min.	Max.	Mean	No. Cases	Min.	Max.	Mean	No. Cases	Min.	Max.	Mean	No. Cases	Min.	Max.	Mean	No. Cases	Min.	Max.	Mean	No. Cases	Min.	Max.	Mean
I	158	−1.0	2.5	0.94	164	0	3.0	1.15	165	0	17.0	5.58	165	0	15.0	4.34	—	—	—	—	195	−0.1	0.1	—	143	−2.0	6.0	2.23
II	158	0	2.5	1.63	165	0	5.5	1.95	165	1.0	25.0	10.04	165	0	8.5	2.99	—	—	—	—	197	−0.1	0.2	—	143	0	7.0	2.84
III	158	−1.0	2.0	0.80	165	0	9.0	3.26	164	1.0	24.0	8.91	164	0	6.5	2.18	—	—	—	—	197	−0.2	0.2	—	143	−3.0	5.0	0.73
aVR	158	−2.5	1.5	−1.09	165	0	13.0	5.92	165	0	9.0	2.32	165	0	18.0	7.45	—	—	—	—	197	−0.1	0.1	—	143	−5.0	2.0	−2.39
aVL	158	−1.5	1.5	0.22	164	0	5.5	1.34	165	0	10.0	3.33	165	0	16.0	5.23	—	—	—	—	197	−0.1	0.1	—	143	−1.5	3.5	0.97
aVF	158	−1.0	3.0	1.17	165	0	6.0	2.36	165	1.5	21.5	8.15	165	0	7.5	2.29	—	—	—	—	197	−0.05	0.2	—	143	−2.0	5.0	1.68
V₁	155	−1.0	2.5	0.69	186	0	0	0	137	3.0	29.0	13.61	123	0	28.0	8.57	142	3.0	50.0	22.73	161	−0.2	0.1	—	126	−8.0	6.0	−2.65
V₂	139	0	2.5	1.13	186	0	0	0	137	3.0	43.0	19.98	121	1.0	42.0	18.35	162	3.0	66.0	40.14	159	−0.2	0.2	—	126	−9.0	9.0	−2.84
V₃	115	0	3.0	1.44	117	0	3.0	1.09	114	5.5	40.0	20.49	112	1.0	39.0	17.72	116	(18.0)†	73.0	38.71	116	−0.2	0.25	—	116	−7.0	6.0	−1.37
V₄	142	0	2.0	1.05	161	0	3.0	1.32	139	3.0	37.0	21.21	123	0	42.0	11.88	146	4.0	63.0	31.73	157	−0.1	0.2	—	123	−7.0	6.5	2.46
V₅	122	0	2.0	1.14	122	0	5.5	2.09	118	3.0	34.0	14.49	119	0	30.0	7.00	121	5.0	48.0	21.89	121	—	0.2	—	122	−4.0	7.0	2.98
V₆	141	0	2.0	0.84	142	0	5.0	1.64	119	3.0	24.0	8.00	138	0	30.0	2.72	161	3.0	34.0	12.17	161	—	0.1	—	125	−3.0	6.0	2.27

* This table is taken from *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels*, fifth edition, published by the New York Heart Association. It is based on normal series studied by Ziegler.

† 6 months–1 year age group only.

figures are presented respectively for the age groups 0 to 1 year, 1 year to 10 years, 10 to 20 years, and 20 years and over (figs. 1–5). There is some slight overlap at the division between the first and second decades because of the form in which some of the original material appeared. The first year was separated from the first decade because several of the infantile features of the electrocardiogram tend to dis-

the maximum, the difference between the former two will be smaller than the difference between the latter two. Under these circumstances it must be clear that the maximum values given will be relatively infrequent in a normal series. For example the maximum Q wave in leads II and III in table 7 is given as 0.4 mv. Actually this value occurred only once in each of these leads, and both in the same

TABLE 3.—*Summary of Various Normal Series Used in the Preparation of Tables 4 to 7*

Author	Subjects			Position	Galvanometer	Precordial Electrode	Leads
	No.	Age (Years)	Sex				
Kossmann and Johnston,[20] 1935	30	20 to 35	M	Supine	Einthoven String (with amplifier)	Circular, 1 cm. diameter	I, II, III; V_R, V_L, V_F; V_1 to V_5, and V_E*
Deeds and Barnes,[24] 1940	100	17 to 47	50 M	Sitting (majority)	Victor Model A (G.E.)	—	I, II, III‡
Kossmann and Goldberg,[25] 1940	35	17 to 41	M	Supine	Cambridge String (with amplifier)	Circular, 2.9 cm. diameter	I, II, III, V_R, V_L, V_F; V_1 to V_6
Wilson and Nyboer,[3] 1938	104	20 to 30	M	Supine	Cambridge String	—	I, II, III
Myers, Klein, Stofer, and Hiratzka,[26] 1947	52 (necropsied)	19 to 87	36 M 16 F	Supine (majority)	Cambridge String	Circular, 2.9 cm.	I, II, III; aV_R, aV_L, aV_F; V_1, V_3, V_5; in 27 subjects V_2, V_4, V_6 also
Vaquero, Limón, and Limón,[27] 1947	500	Newborn to 60	M and F	Supine	Sanborn Instomatic Cardiette	Circular, 2.5 cm. diameter	I, II, III; aV_R, aV_L, aV_F§; V_1 to V_6
Kneese de Melo,[28] 1948	198†	1½ to 40	—	Supine	—	—	aV_R, aV_L, aV_F
Switzer and Besoain,[29] 1950	52	Under 5 to 15	35 M 17 F	Supine	Sanborn Cardiette	—	I, II, III; aV_R, aV_L, aV_F; V_1 to V_6; V_7, V_3R, V_4R
Yu, Joos, and Katsampes,[30] 1951	100	8 days to 14	56 M 44 F	Supine	Edin Direct Writer	Circular, 2.0 cm. diameter (under 5 yrs.); 3.0 cm. diam. (over 5 yrs.)	I, II, III; aV_R, aV_L, aV_F; V_1 to V_6
Sokolow and Friedlander,[22] 1951	150	1 to 60+	M and F	Supine	Sanborn Instomatic Cardiette	Circular 2.8 cm. diameter	aV_R, aV_L, aV_F; V_1 to V_6
Ziegler,[6] 1951	635	Newborn to 16	M and F	Supine	Cambridge String (Hindle and Research)	Circular, 1.5 cm. diameter	I, II, III (553 subjects); aV_R, aV_L, aV_F (553 subjects); V_1 to V_6 (387 subjects); V_4R and V_E* (85 subjects)

* Tip of ensiform.
† 23 subjects under one year of age omitted involuntarily from table 4.
‡ Only data on S-T segment in bipolar extremity leads used.
§ Resistors not used in recording extremity potentials.

appear sometime during this period. A similar table was prepared for the first six months of life but did not differ sufficiently from table 4 to warrant separate presentation.

The minima, maxima, and means are given in each table, the last having been corrected in each instance in accordance with the number of variates presented by each investigator. These statistics are not as useful as they might be because of the tendency of all distribution curves of electrocardiographic deflections to be positively skewed. This means that in a table simply showing the minimum, the mean, and

individual out of the 505 subjects studied. He is normal, as evidenced by a follow-up of 21 years, but there is little question that such a deflection is more often abnormal than the reverse.

The tables fail to disclose the high incidence of late R or R′ deflections in lead V_1 seen in children.[6] A discussion of the significance of these in relation to the width of the QRS interval and to the entire problem of relative and absolute block of the right bundle branch is beyond the scope of this presentation.

TABLE 5.*—*Normal Children, 1 to 10 Years Old, Supine. Size of the Electrocardiographic Deflections in the Bipolar Extremity, Augmented Unipolar Extremity, and Unipolar Precordial Leads Is Given in Tenths of a Millivolt*

Lead	P				Q				R				S				RS				S-T				T			
	No. Cases	Min.	Max.	Mean	No. Cases	Min.	Max.	Mean	No. Cases	Min.	Max.	Mean	No. Cases	Min.	Max.	Mean	No. Cases	Min.	Max.	Mean	No. Cases	Min.	Max.	Mean	No. Cases	Min.	Max.	Mean
I	225	0.5	2.5	1.04	227	0	2.5	1.11	223	1.5	17.0	6.75	225	0	8.0	2.88	—	—	—	—	227	−1.0	1.0	—	223	1.0	6.5	2.53
II	224	0	3.0	1.63	228	0	5.4	1.55	223	2.0	28.0	12.21	223	0	6.5	2.38	—	—	—	—	227	−1.0	2.0	—	223	0	7.0	3.25
III	224	−1.5	2.0	0.62	227	0	8.0	2.50	223	1.0	23.0	7.99	223	0	9.0	1.70	—	—	—	—	228	−1.0	1.0	—	223	−3.0	4.0	0.52
aV_R	293	−2.0	0	−1.56	347	0	14.0	5.70	342	0	6.5	1.60	342	0	19.5	7.77	—	—	—	—	227	−1.0	1.0	—	292	−6.0	−0.2	−2.79
aV_L	293	−1.0	2.0	0.32	347	0	4.0	0.84	342	0	11.8	3.15	342	0	11.0	3.72	—	—	—	—	227	−1.0	1.0	—	292	−4.0	4.0	1.10
aV_F	293	−0.6	2.0	1.03	347	0	5.0	1.33	342	0.5	21.0	9.30	342	0	14.0	1.61	—	—	—	—	227	−1.0	1.0	—	292	−1.0	6.0	1.84
V_1	198	−1.0	2.5	0.72	203	0	0	0	198	0.4	20.0	7.15	197	0	36.5	11.02	103	6.5	46.5	28.85	134	−1.0	2.0	—	197	−6.0	3.0	−2.86
V_2	201	−0.6	2.0	0.92	204	0	0	0	192	2.0	28.0	12.90	196	3.0	44.0	18.31	101	9.0	61.0	37.45	133	−1.0	2.5	—	197	−8.5	6.0	−1.91
V_3	182	0.1	2.0	0.80	185	0	1.0	0.44	181	4.0	42.0	14.00	180	0	36.0	13.66	87	14.0	60.0	32.17	118	0	2.5	—	191	−13.0	12.5	1.30
V_4	200	0	1.5	0.73	203	0	6.0	1.21	199	4.0	50.0	20.16	199	0	26.0	7.53	102	13.0	61.0	32.94	133	0	2.0	—	199	−4.0	14.5	4.54
V_5	188	0	1.5	0.62	190	0	8.0	1.53	186	6.0	40.0	18.97	186	0	15.0	3.62	88	15.0	47.0	23.89	88	−1.0	1.2	—	186	0	12.0	4.51
V_6	197	0	1.5	0.61	201	0	5.0	1.47	196	5.0	23.0	11.94	195	0	13.0	1.23	102	5.0	26.0	14.74	93	−1.0	1.0	—	196	0.7	8.5	3.41
V_7	28	0	1.0	0.50	28	0	3.0	0.78	28	5.5	20.0	11.13	28	0	5.5	1.29	—	—	—	—	28	0	0.8	—	28	0.7	6.5	3.50
V_{3R}	28	−0.8	1.5	0.57	28	0	2.0	0.09	28	1.3	9.9	4.18	28	0	19.5	5.51	—	—	—	—	28	0	0.6	—	28	−4.8	0.9	−1.77
V_{1R}	28	−0.4	1.5	0.44	28	0	2.0	0.09	28	1.0	4.8	2.80	28	0	10.5	8.67	—	—	—	—	28	0	0.4	—	28	−4.9	−1.0	−1.59

* This table is taken from *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels*, fifth edition, published by The New York Heart Association. It is based on normal series studied by Ziegler; Switzer and Besoain; Kneese de Melo; and Yu, Joos, and Katsampes. The table includes a few subjects between 10 and 11 years of age.

Relative Size

Attempts have been made in the past to relate the size of one deflection to another.[31, 32, 33] This has involved principally the Q wave which has been expressed as a percentage of the R wave in the same or other leads. With the increased use of unipolar extremity leads by which the positional origin of a Q wave in the bipolar leads can in many instances be readily

reduced for reasons similar to those given under "Relative Size."

VECTORS

The accuracy of normal data on electrocardiographic deflections regarded as vectors is dependent on all of the variables considered earlier plus an additional error of measurement resulting from the calculation of the magnitude and direction of the vector.

TABLE 6.*—*Normal Adolescents, 10 to 20 Years Old, Supine. The Size of the Electrocardiographic Deflections in the Bipolar Extremity, Augmented Unipolar Extremity, and Unipolar Precordial Leads Is Measured in Tenths of a Millivolt*

Lead	No. Cases	P			Q			R			S			T		
		Min.	Max.	Mean	Min.	Max.	Mean	Min.	Max.	Mean	Min.	Max.	Mean	Min.	Max.	Mean
I	124	0.2	1.5	0.74	0	2.5	0.30	1.3	13.0	5.26	0	6.8	1.40	0.2	5.0	2.32
II	124	0	2.1	1.01	0	2.8	0.37	2.9	20.0	9.66	0	6.3	1.59	0.2	6.5	2.89
III	124	−1.0	1.8	0.43	0	4.6	0.50	0.7	15.8	6.05	0	9.0	1.18	−1.9	3.9	0.65
aV$_R$	214	−1.75	−0.2	−1.03	0	13.7	2.68	0	8.0	1.39	0	17.0	4.94	−5.2	−0.1	−2.36
aV$_L$	214	−1.0	1.4	0.29	0	4.2	0.34	0	10.1	2.24	0	14.2	2.51	−2.5	3.6	0.87
aV$_F$	214	−0.8	2.2	0.74	0	3.8	0.42	1.0	21.0	8.22	0	4.9	0.99	−0.5	5.4	1.76
V$_1$	138	−0.2	2.2	0.77	0	1.5	0.01	0.4	16.7	5.29	0	26.6	11.99	−3.5	7.5	0.22
V$_2$	139	−0.2	2.0	0.78	0	0	0	0.5	23.5	8.16	2.6	45.5	15.81	−3.8	14.1	2.19
V$_3$	138	0	1.8	0.73	0	0.7	0.01	1.6	26.0	10.15	0.9	31.1	12.76	−3.7	13.5	3.39
V$_4$	139	0	1.5	0.62	0	4.4	0.21	3.1	31.6	13.98	0.2	22.2	8.27	−2.8	12.6	4.43
V$_5$	139	0	1.2	0.55	0	3.1	0.49	4.2	29.0	13.56	0	15.1	3.03	0.1	10.5	3.71
V$_6$	138	0	1.0	0.50	0	4.2	0.66	3.5	25.0	11.44	0	11.3	1.74	0.	7.8	3.04
V$_7$	24	0.2	0.8	0.4	0	2.5	0.9	5.0	16.0	15.0	0	5.4	0.9	0.7	5.0	2.4
V$_{3R}$	24	—	1.2	0.7	0	0	0	1.5	8.0	3.8	0	16.0	7.6	−3.6	1.8	−1.1
V$_{4R}$	24	—	1.0	0.4	0	1.5	—	0.7	5.5	2.3	1.0	9.5	5.4	−2.4	1.1	−1.1

* This table is taken from *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels,* fifth edition, published by the New York Heart Association. It is based on normal series studied by Vaquero, Limón and Limón; Switzer and Besoain; Kneese de Melo; Yu, Joos, and Katsampes.

spotted, the usefulness of such relative normal values as have been established has diminished greatly.

Width or Duration

The width of deflections has some value in diagnosis, and therefore a normal value is desirable. The P wave is usually regarded as having a maximum normal duration of 0.1 second. When wider than this it is spoken of as a *broad P wave.* A Q wave has been given significance in the past if its width is 0.04 second or more,[34] but the significance of this normal is

Calculations by one method are not exactly comparable to calculations by another. The planimetric area method[53] of determining the magnitude and direction of these vectors is the most precise but also the most laborious and time consuming. It is not unreasonable to hope that with time and improved methodology the normal length and spatial position of vectors will be easily determined. This should greatly reduce the normal variability which now accrues from a study of the frontal projections only. Gross estimates of the spatial ventricular gradient, the spatial mean mani-

TABLE 7.*—Normal Adults, 20 Years Old and Over, Supine. Size of the Electrocardiographic Deflections in the Bipolar Extremity, Augmented Unipolar Extremity, and Unipolar Precordial Leads, Is Given in Tenths of a Millivolt

Lead	P				Q				R				S				RS or QR				S-T				T			
	No. Cases	Min.	Max.	Mean	No. Cases	Min.	Max.	Mean	No. Cases	Min.	Max.	Mean	No. Cases	Min.	Max.	Mean	No. Cases	Min.	Max.	Mean	No. Cases	Min.	Max.	Mean	No. Cases	Min.	Max.	Mean
I	475	0	2.5	0.69	505	0	2.0	0.27	505	0.7	19.4	5.51	505	0	6.4	1.27	63	3.0	20.6	8.54	100	-0.3	0.9	0.11	505	-0.5	5.6	2.20
II	475	0	3.0	1.07	505	0	4.0	0.38	505	0.5	28.0	9.41	505	0	8.2	1.36	63	8.0	32.0	15.14	100	-1.0	1.0	0.21	505	0	8.0	2.67
III	475	-0.8	2.0	0.56	505	0	4.0	0.48	505	0	22.0	5.56	505	0	13.0	1.29	63	3.2	25.0	10.62	100	-0.6	0.8	0.04	505	-2.0	5.5	0.77
V$_R$	32	-1.0	-0.5	-0.63	62	0	8.0	2.48	62	0	3.0	0.90	62	0	11.0	3.01	62	3.5	12.0	6.50	32	0	0	0	62	-4.0	-0.5	-1.65
V$_L$	32	-0.5	0.5	0.07	62	0	1.5	0.16	62	0	7.0	1.21	62	0	7.0	2.04	62	0.5	8.5	3.37	32	0	0	0	62	-1.0	1.5	0.29
V$_F$	32	0	2.0	0.72	62	0	2.0	0.30	62	0	15.0	6.82	62	0	6.5	0.74	62	3.5	16.5	7.77	32	0	0	0	62	0	4.6	1.40
aV$_R$	411	-1.5	-0.1	-0.79	552	0	16.8	2.38	552	0	4.1	0.94	552	0	15.7	3.76	—	—	—	—	—	—	—	—	479	-5.5	-0.2	-2.40
aV$_L$	411	-1.0	1.4	0.51	552	0	3.5	0.27	552	0	10.1	2.61	552	0	11.3	1.35	—	—	—	—	—	—	—	—	479	-4.0	6.0	0.78
aV$_F$	411	-1.8	1.7	0.74	552	0	3.0	0.38	552	0	20.0	4.73	552	0	7.1	0.81	—	—	—	—	—	—	—	—	479	-0.6	5.2	1.85
V$_1$	371	-1.1	2.2	0.57	567	0	0	0	567	0	15.5	3.09	567	0.8	26.2	9.44	63	6.6	35.0	14.99	33	0	0.5	0.01	542	-4.0	12.2	0.84
V$_2$	371	-0.7	2.0	0.60	594	0	0	0	594	0	23.0	5.96	594	0	39.2	14.09	63	13.0	55.0	26.82	33	0	1.0	0.09	542	-2.6	18.0	4.70
V$_3$	371	-0.5	2.0	0.61	567	0	1.5	0.01	567	0.7	54.6	8.93	567	0	27.5	9.51	63	11.1	54.6	24.12	33	0	2.0	0.20	542	-2.0	21.0	5.16
V$_4$	371	-0.2	2.3	0.60	594	0	4.0	0.13	594	1.8	46.0	13.78	594	0	28.8	5.93	63	9.0	51.6	26.16	33	0	1.0	0.03	542	-0.5	17.0	5.06
V$_5$	371	0	2.4	0.56	567	0	3.4	0.43	567	0.4	33.6	12.01	567	0	16.1	1.96	63	10.0	36.4	19.31	33	0	0	0	542	0	11.0	3.83
V$_6$	371	0	1.8	0.54	564	0	2.7	0.44	564	2.0	22.6	9.68	564	0	14.3	1.00	33	7.0	24.5	13.93	33	0	0	0	512	0	6.9	2.80
V$_E$†	—	—	—	—	30	0	0	0	30	2.0	12.8	5.81	30	0	16.2	6.09	30	5.6	24.2	11.91	30	—	—	—	30	0.2	5.2	2.55

* This table is taken from Nomenclature and Criteria for Diagnosis of the Heart and Blood Vessels, fifth edition, published by the New York Heart Association. It is based on normal series studied by Kossmann and Johnston; Kossmann and Goldberg; Wilson and Nyboer; Vaquero, Limón, and Limón; Deeds and Barnes; Myers, Klein, Stofer, and Hiratzka; Sokolow and Friedlander; Kneese de Melo.

† V$_E$, lead from tip of the ensiform cartilage.

lest potential of QRS, and the spatial mean manifest potential of the T wave can be made by the method of Grant and Estes.[2]

This vectorial approach has simplified clinical electrocardiography and been of considerable value in teaching and in diagnosis. Of particular use is the fact that the normal angle between the QRS and T vectors is said not to exceed 50 degrees in space.[2]
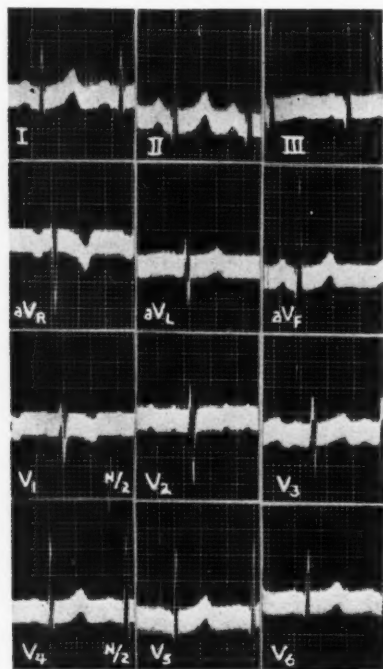

Fig. 3. Normal white female child, age 6 years. The feature worthy of note is the diphasic T wave in lead V_2. Symbols, string sensitivity and time lines as in figure 2.

The QRS Vector

The deflections resulting from depolarization of the ventricular muscle have from the time of Einthoven[35] been treated as a vector projection on the frontal plane described as the mean manifest potential of QRS or the "electrical axis." The vector has magnitude determined from the area of QRS which averages 22 microvolt seconds (μvs) in adults, and 16.6 μvs in children under 15 years of age.[36] Its mean direction in terms of the angle alpha

is approximately 40 degrees and 60 degrees in each of these groups (table 8). The range, however, is an extreme 243 degrees varying from −53.3 degrees in adults[36] and proceeding in a clockwise manner around the usual electrocardiographic arc to an angle of −170 degrees in infants.[6] Even if a careful mean were calculated and a range for 95 per cent of normals established by adding two standard deviations to either side, the range would be so great as to be almost useless. Normal ranges for different age groups could and have been
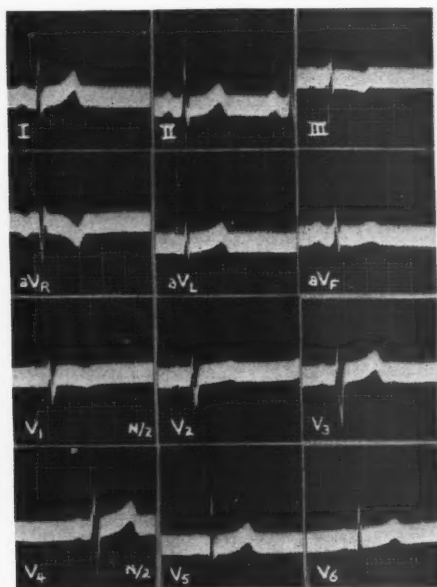
Fig. 4. Normal white male, age 18 years. Symbols, string sensitivity and time lines as in figure 2.

worked out but do not appreciably help except to show that the average "electrical axis" tends to be to the right or vertical in childhood and youth, more horizontal in old age.

Under the circumstances it would appear that not much in the way of a precise statistic for differentiating the normal from the abnormal is likely to be forthcoming. It has seemed rational for clinical purposes to use a simple, standardized nomenclature for the direction of the axis of QRS. If a patient has an electrocardiogram which is normal except for an angle alpha of −30 degrees, he and his

doctor are both interested not so much in the relation of this measurement to a normal statistic as they are in whether the patient does or does not have heart disease. When dealing with an individual the answer to the question can be made only by recourse to methods other than the statistical.

These limitations being forced on it, the Criteria Committee of the New York Heart Association[4] has adopted three simple descriptive groups for the electrical axis of QRS based on the angle alpha. These are: no deviation of the electrical axis, left deviation of the electrical axis, and right deviation of the electrical axis. The first applies when the angle alpha is between 30 and 90 degrees, respec-

three subdivisions are normal or abnormal. This approach has been used to discourage, so far as possible, the unfortunate and widespread practice of making cardiac rather than electrocardiographic diagnoses from the electrocardiogram. It is sincerely hoped that past and future users of the "Criteria" will comprehend that the primary function of the electrocardiographic section is to standardize nomenclature and criteria for electrocardiographic diagnoses, not limits of normality.

The QRS-T Vector (ventricular gradient or G)

The ventricular gradient is at present treated as an octantal vector in space, which is the sum of the QRS and T vectors. Most of the

TABLE 8.—*Statistics of the Magnitude and Direction of the Frontal Projections* ($\hat{A}_{QRS}$, $\hat{A}_{QRST}$) *of the Spatial Electrical Axes of QRS and QRST (after Ashman[36])*

Vector	Subjects and Age in Years	No. and Sex	Size in microvolt seconds (uvs)			Direction in degrees		
			Mean ($\bar{x}$)	Stand. Dev. (S_x)	Range ($\bar{x} \pm 2S$)	Mean (x)	Stand. Dev. (S_x)	Range ($\bar{x} \pm 2S_x$)
$\hat{A}_{QRS}$	Adults 15 to 50+	80 M 84 F	21.8 22.0	10.3 8.5	1.2 to 42.4 5.0 to 39.0	41.7*	31.6	−21.5 to 104.9
	Children 2 to 14	35 M 43 F	16.6	—	—	61.1†	20.5	20.1 to 102.1
$\hat{A}_{QRST(G)}$	Adults 15 to 50+	80 M 84 F	47.1 45.4	18.1 14.7	10.9 to 83.3 16.0 to 74.8	44.8 33.8	18.7 18.3	7.4 to 82.2 −2.8 to 70.4
	Children 2 to 14	38 M 43 F	46.4	14.9	16.6 to 76.2	48.0	12.5	23.0 to 73.0

* 157 adults only.   † 77 children only.

tively; the second between 29 and −89 degrees; the third between 91 and −91 degrees. The smallest polar angle between each set of figures is the one that applies.

By way of digression, this procedure of suggesting a standardized nomenclature where an exact and clinically useful statistic is wanting has been misinterpreted on several occasions[17, 54] as meaning that the limits defined are the normal limits. A careful reading of the electrocardiographic section of the "Criteria"[4] will reveal that, with two exceptions, terminology has been purposely designed to avoid, so far as possible, the implication of normality or abnormality. With regard to the electrical axis of QRS the nomenclature adopted is descriptive; it does not indicate which of the

data collected on it are concerned with its frontal projection. As a vector it has magnitude usually expressed in microvolt seconds (μvs) or in Ashman units (A.U.) which are 4 μvs each. The direction is expressed as an angle alpha as for the QRS vector.

When the ventricular gradient was first described[37] great expectations were entertained for its eventual clinical usefulness. To date these have not been fully realized for several reasons. One is the difficulty involved in determining it. Measurement of areas of QRS and T waves is time-consuming if done accurately. The range of normal is quite wide both in manifest magnitude and direction, but not as wide, theoretically and actually, as similar measurements on the QRS vector.

Ashman and his associates[38] have in part overcome this by establishing the spatial relationships, at least in the normal subject, of the vectors of QRS, QRS-T or G, and of the anatomic axis of the ventricles or H. Their
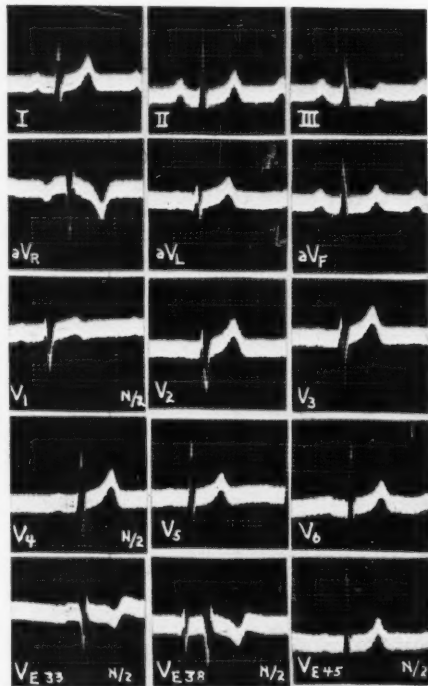

FIG. 5. Normal white male, age 26 years. In addition to the surface leads, eosphageal leads were recorded at supra-atrial (V_{E33}), atrial (V_{E38}), and ventricular (V_{E45}) levels. The symbol V_E means potential of the esophagus, and the arabic number indicates the distance of the exploring electrode from the anterior nares. The similarity of lead V_6 to lead V_{E45} is to be noted. Other symbols and time lines as in previous figures. When recording the precordial and esophageal leads the tension of the string was adjusted so that 1 mv. = 0.5 cm. (From *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels*, fifth edition, published by the New York Heart Association.)

calculations indicate that the relations of the electrocardiographic vectors to the ventricular muscle mass are quite constant in space with an approximate angle between H and QRS of 90 degrees and between H and G of 60 degrees. In order to predict what the direction of the

gradient should be in any individual, the anatomic axis of the ventricles must first be estimated either from the electrocardiogram[39] or the roentgenogram and the frontal vectorcardiographic loop constructed. Finding H and accepting the fixed relations of vectorial QRS-T to it, a prediction with a model loop can be made of what G should be.[40] In normal subjects the measured frontal gradient does not deviate (or diverge) from the predicted by more than 23 degrees to the left or 15 degrees to the right of the estimated vector. Though the method has been very illuminating from the viewpoint of fundamental electrocardiography, it is quite cumbersome to use clinically. Further, when the vectorcardiographic loop is changed greatly by disease or hypertrophy, the very situations in which the clinician is most interested, the method is not applicable.

Grossly, the orientation in the frontal plane of vector G to the vector of QRS will depend much on the electrical and anatomic positions of the heart. If the heart is vertical, $\hat{G}$ will usually be to the left of $\hat{A}_{QRS}$; if horizontal, to the right; and in either case will not deviate in the direction indicated by an angle much greater than 30 degrees.[41] This can be made use of clinically in a gross way with or without the presence of intraventricular block. If the vector G is not roughly parallel to QRS with a leeway of 30 degrees in the proper direction, it is probably abnormal.[2]

Some indication of the ranges of the normal frontal ventricular gradient are shown in table 8.

The T Vector

Quantitative data on the T vector are not numerous. It is apparent that it is directed quite far to the right or is vertical (mean angle alpha 77 degrees) in the first 24 hours of life and gradually approaches an angle of approximately 40 degrees up to adolescence.[6] During most of this period it is also directed backward as is evidenced by the inverted T waves which normally occur in leads V_1 to V_4 in infants and children (tables 4 and 5) and occasionally in older individuals (tables 6 and 8). Beyond adolescence its direction in space is forward and

to the left but quite variable so far as the latter direction is concerned.[2] Due to the existence of a gradient in the duration of the excited state, this T vector usually has a direction similar to the QRS vector. As noted earlier the spatial angular separation of the two is said not to exceed 50 degrees.[2]

Because of limitations with regard to exact measurements, a procedure for gross description has been adopted as for the QRS vector. So far as the frontal plane is concerned, vectorial T is said to show no deviation, left deviation or right deviation of its electrical axis with the same angular limits defined for these as in the case of the QRS vector.

The S-T Vector

Normally a minute or no electromotive force is present at the time the junction between QRS and S-T is written in the electrocardiogram (tables 4 to 7). This junction is often called "J" to distinguish it from the S-T segment, but by custom the "S-T vector" is calculated from any displacement of J that may exist.

Vectorcardiography

Although the form of the normal vector cardiogram in several planes is fairly well known, a definition of it at this time is not easily made because of the great variety of technics available for recording it directly.[42-49] A basic problem is involved, namely, which method will most accurately provide the true rectilinear components of the spatial record. Until this is solved more satisfactorily than it has been up to now, an attempt to define the normal seems premature.

SPECIAL LEADS

Esophageal Leads

The most comprehensive information of a quantitative kind on esophageal leads has been collected by Kistin, Brill, and Robb.[50] The records obtained can be divided into three groups, the *atrial*, the *transitional*, and the *ventricular*, depending upon the form of the atrial and ventricular deflections. The first type is obtained when the esophageal electrode is 32.5 to 47.5 cm. from the anterior

nares; the second between 40.0 and 50.0 cm. from the nares, and usually 2.5 to 5.0 cm. below the lowest atrial level; the third 42.5 to 52.5 cm. or more from the nares. For details the reader is referred to the original article. Perhaps of greatest significance is that a Q wave deeper than 0.4 mv., or more than 25 per cent of the R wave in the same ventricular lead[33, 51] is not uncommon in the normal subject.

Intracardiac Leads

Measurements have been made of the size of the RS deflection in the right atrium, the right ventricle, and attached vessels of 14 normal subjects.[52] The approximate relative sizes of these deflections, regarding the mean of 11.7 mv. in lead II as a unit reference, were as follows:

Lead	Relative Size
II	1.0
Right Pulmonary Artery	1.1
Superior Vena Cava	1.2
Right Atrium (all levels)	1.5
Pulmonary Artery	1.8
Leads V_2 to V_4	2.0
Right Ventricle {Base	3.5
Right Ventricle {Midventricle	5.7
Right Ventricle {Apex	8.6

SUMMARY

An attempt has been made to show that the data available are not altogether adequate for establishing exact criteria for the normal electrocardiogram. Some of the more recent efforts to correct this situation have been reviewed and synthesized so far as possible into a form which it is hoped may be immediately useful. It is emphasized that this report is merely of recent clinical progress in the field. A more comprehensive and statistically complete investigation of the normal electrocardiogram in all age groups remains to be done.

REFERENCES

[1] ZIEGLER, R. F.: A note on the importance of proper technique in the recording of the precordial electrocardiogram. Am. Heart J. **35:** 769, 1948.

[2] GRANT, R. P., AND ESTES, JR., E. H.: Spatial Vector Electrocardiography. Philadelphia, Blakiston, 1951.

[3] WILSON, F. N.: Recent progress in electrocar-

diography and the interpretation of borderline electrocardiograms. Tr. A. Life Insur. M. Dir. America **24**: 96, 1937.

4 CRITERIA COMMITTEE OF THE NEW YORK HEART ASSOCIATION: Nomenclature and Criteria for Diagnosis of Diseases of the Heart, ed. 5. New York, New York Heart Association, 1953.

5 GRAYBIEL, A., MCFARLAND, R. A., GATES, D. C., AND WEBSTER, F. A.: Analysis of the electrocardiograms obtained from 1000 young healthy aviators. Am. Heart J. **27**: 524, 1944.

6 ZIEGLER, R. F.: Electrocardiographic studies in normal infants and children. Springfield, Ill., Charles C Thomas, 1951.

7 WHITE, P. D., LEACH, C. E., AND FOOTE, S. A.: Errors in measurements of the P-R (PQ) interval and QRS duration in the electrocardiogram. Am. Heart J. **22**: 321, 1941.

8 SAVILAHTI, M.: On the normal and the pathological PQ time of the electrocardiogram. Acta med. scandinav. **123**: 252, 1946.

9 SCHLAMOWITZ, I.: An analysis of time relationships within the cardiac cycle in electrocardiograms of normal men. III. The duration of the P-R interval and its relationship to the cycle length (R-R Interval). Am. Heart J. **31**: 473, 1946.

10 SAVILAHTI, M.: Concerning the effect of frequency and of age on the QRS time of the electrocardiogram. Acta med. scandinav. **123**: 143, 1946.

11 TARAN, L. M., AND SZILAGYI, N.: Technical considerations in the measurement of the electrical systole (QT interval) and its relationship to the electrical events in the cardiac cycle. I. The end of the T wave. Bull. St. Francis Sanatorium **9** (No. 1): 15, 1952. II. The effect of cardiac rate upon the duration of the electrical systole. Bull. St. Francis Sanatorium **9** (No. 2): 15, 1952. III. The effect of cardiac rate upon the duration of the electrical systole—sinus bradycardia, regular sinus rhythm, sinus tachycardia. Bull. St. Francis Sanatorium **9** (No. 3): 15, 1952.

12 LEPESCHKIN, E., AND SURAWICZ, B.: The measurement of the Q-T interval of the electrocardiogram. Circulation **6**: 378, 1952.

13 —: Modern Electrocardiography. Baltimore, Williams & Wilkins, 1951. Vol. I.

14 BAZETT, H. C.: An analysis of the time relations of the electrocardiogram. Heart **7**: 353, 1918.

15 ASHMAN, R., AND HULL, E.: Essentials of Electrocardiography, ed. 1. New York, Macmillan, 1937.

16 WHITE, M. S., KOSSMANN, C. E., AND ERSHLER, I.: The effect of high altitude and of rebreathing on the duration of electrical systole in man. Am. Heart J. **24**: 230, 1942.

17 STEWART, C. B., AND MANNING, G. W.: A detailed analysis of the electrocardiograms of 500 R.C.A.F. aircrew. Am. Heart J. **27**: 502, 1944.

18 CHEER, S., AND LI, R. C.: Studies on the electrical systole (Q-T interval) of the heart. I. The duration of electrical systole in normal Chinese. Chinese J. Physiol. **4**: 191, 1930.

19 KOSSMANN, C. E.: Unipolar electrocardiography, including intracardiac leads, in the diagnosis of myocardial disease. Bull. New York Acad. Med. **26**: 20, 1950.

20 —, AND JOHNSTON, F. D.: The precordial electrocardiogram. I. The potential variations of the precordium and of the extremities in normal subjects. Am. Heart J. **10**: 925, 1935.

21 SODI PALLARES, D., PARÁS, O., CABRERA COSÍO, E., AND MENDOZA, F.: La deflexión intrínseca en casos normales y en hipertrofias ventriculares. Arch. Inst. cardiol. México **16**: 397, 1946.

22 SOKOLOW, M., AND FRIEDLANDER, R. D.: The normal unipolar precordial and limb lead electrocardiogram. Am. Heart J. **38**: 665, 1949.

23 ELECTROCARDIOGRAPHIC COMMITTEE OF THE AMERICAN HEART ASSOCIATION: Standardization of electrocardiographic nomenclature. J.A.M.A. **121**: 1347, 1943.

24 DEEDS, D., AND BARNES, A. R.: The characteristics of the chest lead electrocardiograms of 100 normal adults. Am. Heart J. **20**: 261, 1940.

25 KOSSMANN, C. E., AND GOLDBERG, H. H.: Unpublished observations.

26 MYERS, G. B., KLEIN, H. A., STOFER, B. E., AND HIRATZKA, T.: Normal variations in multiple precordial leads. Am. Heart J. **34**: 785, 1947.

27 VAQUERO, M., LIMÓN, R., AND LIMÓN, A.: Electrocardiograma normal—estudio de 500 casos en derivaciones standard y unipolares. Memorias del Segundo Congreso Interamericano de Cardiología **2**: 887, 1948.

28 KNEESE DE MELO, H.: Aspectos normais das derivações unipolares das extremidades. Arq. bras. cardiol. **1**: 237, 1948.

29 SWITZER, J. L., AND BESOAIN, M.: Electrocardiograms of normal children with special reference to the aV limb leads and chest leads. Am. J. Dis. Child. **79**: 449, 1950.

30 YU, P. N. G., JOOS, H. A., AND KATSAMPES, C. P.: Unipolar electrocardiograms in normal infants and children. Am. Heart J. **41**: 91, 1951.

31 PARDEE, H. E. B.: The significance of an electrocardiogram with a large Q in Lead III. Arch. Int. Med. **46**: 470, 1930.

32 KOSSMANN, C. E., SHEARER, M., AND TEXON, M.: The initial ventricular deflection in the electrocardiograms of normal subjects. Am. Heart J. **11**: 346, 1936.

33 MYERS, G. D., AND OREN, B. G.: The use of the augmented unipolar left leg lead in the differentiation of the normal from the abnormal Q wave in standard Lead III. Am. Heart J. **29**: 708, 1945.

34 BAYLEY, R. H.: The significance of the duration

of Q_3 with respect to coronary disease. Am. Heart J. **18**: 308, 1939.

35 EINTHOVEN, W., FAHR, G., AND DE WAART, A.: Über die Richtung und die Manifeste Grosse der Potentialschwankungen im Menschlichen Herzen und über den Einfluss der Herzlage auf die Form des Elektrokardiograms. Arch. ges. Physiol. **150**: 275, 1913.

36 ASHMAN, R.: A statistical study of the ventricular gradient and of the QRS complex of the electrocardiogram. Arch. Inst. cardiol. México **15**: 266, 1945.

37 WILSON, F. N., MACLEOD, A. G., AND BARKER, P. S.: The T deflection of the electrocardiogram. Tr. A. Am. Physicians **46**: 29, 1931.

38 ASHMAN, R., GARDBERG, M., AND BYER, E.: The normal human ventricular gradient. III. The relation between the anatomic and electric axes. Am. Heart J. **26**: 473, 1943.

39 —: Estimation of heart position from the QRS complex. Arch. Inst. cardiol. México **12**: 130, 1946.

40 LA DUE, J. S., AND ASHMAN, R.: Electrocardiographic changes in acute glomerulonephritis Am. Heart J. **31**: 685, 1946.

41 BAYLEY, R. H., HOLOUBEK, J. E., AND BAKER, A. E.: Unpublished observations quoted by Ashman.

42 SCHELLONG, F.: Gründzuge einer klinischen Vektorkardiagraphie des Herzens. Berlin, Springer, 1939.

43 DUCHOSAL, P. W., AND SULZER, R.: La Vectocardiographie. Basel, S. Karger, 1949.

44 BRILLER, S. A., MARCHAND, N., AND KOSSMANN, C. E.: A differential vectorcardiograph. Rev. Scient. Inst. **21**: 805, 1950.

45 ABILDSKOV, J. A., BURCH, G. E., AND CRONVICH, J. A.: The validity of the equilateral tetrahedron as a spatial reference system. Circulation **2**: 122, 1950.

46 GRISHMAN, A., AND SCHERLIS, L.: Spatial vectorcardiography. Philadelphia, Saunders, 1952.

47 JOUVE, A., BUISSON, P., ALBOUY, A., VELASQUE, P., AND BERGIER, G.: La Vectocardiographie en Clinique. Paris, Masson et Cie, 1950.

48 DEN BOER, W.: Vectorcardiographie. Utrecht, Kemink en Zoon N.V., 1951.

49 DONZELOT, E., MILOVANOVICH, J. B., AND KAUFMANN, H.: Etudes Pratiques de Vectographie. Paris, L'expansion Scientifique Francaise, 1950.

50 KISTIN, A. D., BRILL, W. D., AND ROBB, G. P.: Normal esophageal and gastric electrocardiograms. Description, statistical analysis and bearing on theories of "electrocardiographic position." Circulation **2**: 578, 1950.

51 NYBOER, J.: Exploratory electrocardiograms—extremity, precordial, esophageal—and discussion of the Q_3 electrocardiogram. Tr. A. Life Insur. M. Dir. America **30**: 31, 1946.

52 KOSSMANN, C. E., BERGER, A. R., RADER, B., BRUMLÍK, J., BRILLER, S. A., AND DONNELLY, J. H.: Intracardiac and intravascular potentials resulting from electrical activity of the normal human heart. Circulation **2**: 10, 1950.

53 WILSON, F. N., MACLEOD, A. G., BARKER, P. S., AND JOHNSTON, F. D.: The determination and the significance of the areas of the ventricular deflections of the electrocardiogram. Am. Heart J. **10**: 46, 1934.

54 VISCIDI, P. C., AND GEIGER, A. J.: Electrocardiographic observations on 500 unselected young adults at work. Am. Heart J. **26**: 763, 1943.

ABSTRACTS

Editor: SAMUEL BELLET, M.D.

AVITAMINOSIS

Gale, E. T., and Thewlis, M. W.: Vitamins C and P in Cardiovascular and Cerebrovascular Disease. Geriatrics **80:** 8 (Feb.), 1953.

Research has shown that vitamin C plays a vital role in cellular metabolism and in maintaining the integrity of cells. Vitamin P apparently aids vitamin C in reducing capillary fragility. It may be that blood vessels are weakened by a decrease in the cellular content of ascorbic acid. Many instances of hemorrhage and thrombosis in the heart and brain may be avoided if adequate amounts of vitamin P and C are provided. Thirty-two elderly people who had marked vascular symptoms were studied from one to four years. Vitamin C and P, in varying amounts were taken continuously. Of the four patients who died from vascular diseases, not one had taken more than 100 mg. of vitamin C daily. Many symptoms of vascular disturbances in the aged suggest that latent scurvy may be a frequent occurrence. Deficient diets, inadequate absorption, and poor utilization cause deficiencies of ascorbic acid in elderly people. Large amounts of supplementary vitamin C may be necessary.

BERNSTEIN

BACTERIAL ENDOCARDITIS

Winchell, P.: Infectious Endocarditis as a Result of Contamination during Cardiac Catheterization. New England J. Med. **248:** 245, 1953.

An instance of infective endocarditis due to alpha-hemolytic streptococcus occurring in a woman aged 44 years with rheumatic mitral stenosis is described. The first symptoms of the endocarditis appeared 11 days after cardiac catheterization. Penicillin had been given on the evening prior to catheterization, twice on the day of the study and also two days after

the examination. Clinical recovery followed combined penicillin and streptomycin treatment. Studies of the apparatus used in the cardiac catheterization revealed gram-positive and gram-negative rods and cocci in a supposed sterile water and mineral oil mixture filling a leveling bottle in the Hamilton manometer system. Swabs of the interior of the manometer contained similar organisms. It is presumed that the organisms were introduced into the blood stream during the cardiac catheterization.

ROSENBAUM

BLOOD COAGULATION

Quick, A. J., and Hussey, C. V.: Interpretation of the One-Stage Method for Determining Prothrombin Time. New England J. Med. **248:** 624 (Apr. 9), 1953.

In a discussion of the variables in the prothrombin time the authors point out that an excess of labile factor does not shorten the prothrombin time to less than 12 seconds, and it is therefore incorrect to consider the labile factor as an accelerator. The prothrombin time as measured by the standardized one-stage procedure by these workers has been found to be constant in normal subjects, rarely varying from 12 seconds. Any changes must be differentiated from these due to intrinsic or physiologic causes and those due to extrinsic causes such as contact with glass or the addition of various agents other than thromboplastin. These workers postulate that prothrombin exists in an inactive form, prothrombinogen, and an active or free form, prothrombin. This latter function is the only one measured by the unmodified, one-stage procedure. When human plasma is stored, labile factor disappears with prolongation of the prothrombin time. Furthermore, prothrombinogen is converted to free prothrombin by the

catalytic action of a glass surface. The lack of labile factor obscures this increased prothrombin activity in stored plasma, but it becomes evident when labile factor is resupplied. These authors feel that the concept of an active and an inactive prothrombin is more properly applicable to the hypoprothrombinemia from Dicumarol and in the newborn infant than the prothrombin accelerator theory.

ROSENBAUM

Guttas, C. G., Moloney, W. C., and Sise, H. S.: The Effect of Emulsified Vitamin K on Phenyl-indanedione-Induced   Hypoprothrombinemia. Blood **8**: 276 (March), 1953.

Phenylindanedione-induced   hypoprothrombinemia is rapidly counteracted by a vitamin K emulsion. This hypoprothrombinemia is antagonized at a more rapid rate than that induced by any of the other commonly employed prothrombopenic agents. The optimum dose of the vitamin K emulsion in emergency is 5 mg. per kilogram. Since a refractoriness to the prothrombopenic action of phenylindanedione ensues, smaller doses should be used in situations where there is no emergency.

BERNSTEIN

CONGENITAL ANOMALIES

Swan, H.: Surgical Closure of Interauricular Septal Defects. J.A.M.A. **151**: 792 (Mar. 7), 1953.

In 1949 an experimental method for production and closure of interauricular septal defects in dogs was developed. The method of closure involved the inversion of both auricular tips through the septal defect forming a doughnut shaped lumen in each atrium. The experiments showed that (1) the right heart could be opened with cessation of blood flow and intracardiac operations could be performed under direct vision for periods up to one and one-half minutes, (2) both pleural cavities could be opened at operation with impunity, (3) the auricular tips could be inverted without interference with blood flow or danger of intra-auricular thrombosis, and (4) the experimental defects could be occluded from 60 per cent to 100 per cent by this means. Five human patients in advanced stages of the disease have been operated upon by this method. Four patients have tolerated the procedure well. One died postoperatively. A two year follow-up on two patients shows fair clinical improvement in one, good clinical improvement in the other. Patients with interauricular septal defects who demonstrate progressive cardiac enlargement with a marked increase in pulmonary blood flow should be considered candidates for operative therapy.

KITCHELL

Gross, R. E.: Surgical Closure of Interauricular Septal Defects. J.A.M.A. **151**: 795 (Mar. 7), 1953.

With a series of experiments on 130 dogs, Gross studied to find the best possible method of attaching a leak proof rubber well to the right auricular wall. With the use of this well it was found that (1) blood rose in the well only a few centimeters in any instance. (2) Blood in the well could be kept fluid by adding a few cubic centimeters of 0.02 per cent heparin solution every few minutes. (3) The heart tolerated the open well in an extremely satisfactory manner. (4) The peripheral flow of blood tended to fall somewhat just after the well opened but the flow could be maintained if the dogs received blood transfusion to compensate for the amount that had been lost into the well. (5) The well could be kept open indefinitely. (6) Through the pool of blood in the well it was possible to introduce exploring fingers into the right auricle and identify accurately the various landmarks of the interior. (7) At the end of an experiment it was possible to remove the rubber well and to close the auricular wall. After this development the following four methods of closure of interauricular septal defects were studied: (1) An excised auricular appendage was sutured over the auricular septal defect; a serious drawback of this method was the softness of the graft which was too yielding to be felt in the depths of the auricular cavity and hence in some instances was difficult to place. (2) Some interauricular septal defects were plugged by Hufnagel buttons (plastic prostheses consisting of two circular disc-like structures of methyl methacrylate or "kel-F" which could be screwed together, one on one side of the septum and one on the other). (3) Pieces of polyethylene sheeting, or nylon sheeting, a fraction of a millimeter in thickness, could be sewed to the septum with interrupted silk stitches. These sheets were tolerated well and soon became embedded within the substance of the septum. (4) Septal defects that were small (less than 1 cm. in diameter) could be closed by the placement of silk sutures. The experiments convinced Gross that it would be possible to close interauricular defects in man by any of the four methods described, however, the third and fourth methods would be of greatest value. Seven patients were treated by a variety of these methods. In three patients Hufnagel "kel-F" buttons were placed within the heart. The operations were tolerated well but the buttons all worked loose and fell into either the left or right auricular cavities, and all three of these children died within a few weeks. Thus buttons of this type probably have little usefulness in man. In three patients sheets of nylon or polyethylene were used to cover the septal opening. In one patient where the plastic plate was too large, a clot formed which eventually blocked the tricuspid valve and led to death. In the other two cases good results were obtained. In one other child two small septal openings were found and closure was accomplished by sutures of the edge of the septum. This child has done well.

KITCHELL

Selzer, A., and Carnes, W. H.: The Role of Pulmonary Stenosis in the Production of Chronic Cyanosis. Am. Heart J. **45**: 382 (Mar.), 1953.

The incidence and cause of chronic cyanosis was studied in pulmonary stenosis without an intracardiac communication, in pulmonary stenosis with a patent foramen ovale, and in the tetralogy of Fallot. Pulmonary stenosis not associated with an intracardiac communication is a noncyanotic disease and when cyanosis does occur, it is almost always associated with and caused by cardiac failure with stagnant cyanosis. Chronic cyanosis is pulmonary stenosis and patent foramen ovale is almost always present and is due to the anoxemia attendant on the right to left shunt. In the tetralogy of Fallot with a large ventricular septal defect, the systemic circulation must be supported by an elevated resistance within the lesser circulation as a condition for survival, and pulmonary stenosis constitutes one of the available mechanisms for this adjustment, however, it is not the only important factor in the production of anoxemia and cyanosis.

<div align="right">RINZLER</div>

Rogowsky, M., Limbos and Thys: A Case of a Bicephalic Foetus with Two Hearts. Acta cardiol. **8**: 177 (Fasc. 2), 1953.

A rare anomaly is described of a fetus born with two heads living for about two hours. Respiration was initially rhythmic in both heads, with temporary alternation of the two sides; respiration ceased earlier in the left. On auscultation there were regular heart sounds in the usual medial position of the chest, but an electrocardiogram showed two types of ventricular complexes and irregular P waves. At autopsy two hearts were found communicating by the inferior vena cava. The larger right heart gave off the main artery to the lungs and the aorta. The smaller left heart, which had a wide interventricular communication, gave off a rudimentary aorta supplying the corresponding head, and a pulmonary artery draining via a ductus arteriosus into the main aortic trunk.

<div align="right">PICK</div>

Schopf, D.: The Syndrome of Lutembacher. Cardiologia **22**: 129 (Fasc. 3), 1953.

The author reviewed the literature concerning clinical manifestations, anatomic findings and the pathogenesis of Lutembacher's disease and reported two of his own observations with autopsy control. The usual findings at post mortem are a large interatrial communication, an enormous dilatation and hypertrophy of the right ventricle, a huge pulmonary artery, and a more or less narrow aorta. The clinical picture varies considerably. The important diagnostic signs found at x-ray examination are: a cor bovinum with dilatation predominantly to the right, marked prominence of the pulmonary cone, a small left atrium, a small or absent aortic knob, and enlarged, often pulsating hilar shadows. Pulmonary edema and subacute bacterial endocarditis do not occur in Lutembacher's syndrome.

From the pathologic anatomic viewpoint, the two reported cases belonged in two different groups. In the first case, a 47 year old woman, a congenital atrial septal defect was complicated by a typical acquired mitral stenosis. In the second case, an infant who died two days after birth, a stenotic deformation of the mitral ostium appeared to be the primary congenital anomaly which secondarily resulted in a wide patency of the foramen ovale.

<div align="right">PICK</div>

Stiefel, G. E.: Lutembacher Syndrome. Cardiologia **22**: 177 (Fasc. 3), 1953.

Clinical and pathologic anatomic findings are reported in two cases of Lutembacher syndrome and the symptomatologic, embryologic and the pathophysiologic aspects of this condition are discussed. Both patients were, as usual, women—one 37 and the other 64 years old—and both had a good functional capacity until a short time before death. Both had a typical mitral endocarditis of the rheumatic type.

The mitral lesion associated with an atrial septal defect is, according to the author, always acquired. The combination of the two defects results in a left-to-right atrial shunt which prevents cyanosis, hypoxia, the complication of an atrial septal defect, and pulmonary edema, a complication of mitral stenosis. Hence the life expectancy of patients with Lutembachers syndrome is comparatively high.

<div align="right">PICK</div>

Katz, M., Benzier, E. E., Nangeroni, L., and Sussman, B.: Kartagener's Syndrome (Situs Inversus, Bronchiectasis and Chronic Sinusitis). Report of a Case. New England J. Med. **248**: 730, 1953.

An example of Kartagener's syndrome occurring in a 20 year old boy is described. This syndrome consists of situs inversus, bronchiectasis, and chronic sinusitis. It is pointed out that bronchiectasis has a definitely higher incidence in persons with transposition of the viscera than in the general population. The possibility of a congenital factor in the pathogenesis of bronchiectasis is suggested. It is recommended that persons with situs inversus, especially with concomitant sinus infections, be thoroughly investigated for bronchiectasis, including bronchography. It is also suggested that families of patients with Kartagener's syndrome be screened for similar abnormalities.

<div align="right">ROSENBAUM</div>

CONGESTIVE HEART FAILURE

Brown, M. G., Holzman, D., and Creelman, E. W.: Serum Quinidine Levels in Congestive Heart Failure. Am. J. M. Sc. **225**: 129 (Feb.), 1953.

The occurrence of toxic reactions in the form of

ventricular tachycardia following quinidine therapy in congestive failure patients led to a study of the serum quinidine levels after oral administration of the drug to 11 patients with heart failure and 16 normal subjects. Quinidine sulfate, 0.4 Gm., was given orally for three doses at two-hour intervals. Serum quinidine levels were examined between 2 and 12 hours after the last dose by a method described in the paper. The highest concentrations occurred in two to four hours after the last dose; there was no conspicious difference noted in the levels of the two groups. The rate of disappearance thereafter in the controls seemed to follow an exponential decay curve. Serum levels at 12 hours in the heart failure group were generally higher than in those of the control, indicating a slower rate of disappearance. In the failure patients 57 per cent of the peak load remained in 12 hours compared to 30 per cent for the control subjects. Thus, with maintenance quinidine therapy, it is possible for patients with heart failure to develop serious toxic complications because of high serum levels of the drug.

SHUMAN

CORONARY ARTERY DISEASE

Russell, N. G. Jr.: Coronary Disease in the Second Century of Life. Am. J. M. Sc. 225: 241 (March), 1953.

The author examined 9 individuals ranging from 100.5 years to 112 years of age. One had experienced a coronary occlusion at the age of 100 years and expired 9 months later. Minor electrocardiographic abnormalities were present in several of the remaining 8 patients, however, cardiac disease was absent in the latter group. The ingestion of cholesterol-containing foods and the use of tobacco by certain of these patients had not given rise to coronary artery disease.

SHUMAN

Osher, H. L., and Wolff, L.: The Diagnosis of Infarction of the Interventricular Septum. Am. Heart J. 45: 429 (Mar.), 1953.

Thirty-five patients with necropsy evidence of septal infarction and adequate electrocardiographic data were studied. The most common diagnostic features relate to conductive defects and are so diagnostic under the following conditions: when bundle branch block, or high-grade auriculoventricular block appears during the course of acute myocardial infarction. (a) High grade auriculoventricular block indicates involvement of the posterobasal region of the septum. (b) Complete right bundle branch block is associated with conspicuous Q waves in the right precordial leads. (c) Left bundle branch block is associated with Q waves in the left precordial leads. (d) Left bundle branch block is associated with low voltage in the limb and left precordial leads. In the presence of normal intraven-

tricular conduction, QS deflections with abnormally elevated S-T segments in the right precordial leads may indicate acute septal infarction. Electrocardiographic evidence of simultaneous acute anteroseptal and posterior infarction is a characteristic sign of septal infarction.

RINZLER

Lampesis, P. T., Crandall, W. D., and King, S. J.: Ruptured Myocardial Infarct with Survival for Three Weeks. New England J. Med. 248: 455 (Mar. 12), 1953.

A patient, aged 64 years, who had an acute anterior myocardial infarction is described. On the second day after the attack there was a sudden onset of dyspnea, cyanosis, shock, and semiconsciousness. Roentgenographic studies on two occasions during the second week disclosed a cardiac silhouette which suggested a pericardial effusion. A diagnosis of hemopericardium was established by pericardial aspiration done during the third week of the illness. The patient died four weeks after the onset of the attack. The autopsy disclosed a pericardial sac which contained approximately 800 cc. of clotted blood. There was a large zone of infarction in the apex of the left ventricle with a tear 1.5 cm. by 2.0 cm. in its posterolateral aspect. The hemopericardium showed evidence of organization and there was also evidence of terminal hemorrhagic dissection of the myocardium.

ROSENBAUM

PATHOLOGIC PHYSIOLOGY

Lape, H. E., and Maison, G. L.: Cardiac Resuscitation and Survival: Influence of Rate of Manual Compression, Type of Countershock and of Epinephrine. Am. J. Physiol. 172: 417 (Feb.), 1953.

Under ether anesthesia in ventricular fibrillation, the best rate of manual compression of the heart proved to be 25 per minute. Epinephrine and manual compression were unsuccessful in attempts at defibrillation. Single or serial alternating current volleys as well as single direct current pulses and condenser discharges were used successfully in defibrillation. These were successful even though the circulation had been maintained previously only by manual compression and artificial respiration for as long as 20 minutes. Cessation of fibrillation was followed by spontaneous beat in almost all cases. Survival for more than 24 hours was not less likely because many unsuccessful attempts at countershock were made. Ouabain, immediately after defibrillation, improved chances of survival.

OPPENHEIMER

Brigden, W., and Leatham, A.: Mitral Incompetence. Brit. Heart J. 15: 55 (Jan.), 1953.

The authors attempt to determine the natural history, symptoms, and signs of mitral incompetence

on the bases of a review of the literature and of their experience with 30 cases, 10 proved by necropsy.

Individuals with mitral incompetence rarely give a history of rheumatic fever, are more commonly males, and live longer than those with mitral stenosis. Subacute bacterial endocarditis is a frequent complication. Heart failure occurs late and is progressive. Palpitation due to an enlarged left ventricle and multiple premature beats is common. The first sound at the apex is normal and never accentuated. Neither is there evidence of pulmonary hypertension. The systolic murmur is long and may last until the second sound or even longer. The third sound is frequently audible. The electrocardiogram never shows right axis deviation and in one third of the cases had left axis deviation. Rheumatic stigmata were present in only one of nine individuals studied at necropsy.

Twenty-six of the 30 showed enlargement of the left auricle and all 25 individuals studied fluoroscopically showed systolic expansion of the left auricle in both the anterior and oblique views.

SOLOFF

Doyle, J. T., Wilson, J. S., Lepine, C., and Warren, J. V.: An Evaluation of the Measurement of the Cardiac Output and of the So-Called Pulmonary Blood Volume by the Dye-Dilution Method. J. Lab. & Clin. Med. **41:** 29 (Jan.), 1953.

The dye-dilution method of Stewart and Hamilton is a useful technic in measuring the cardiac output. In 152 consecutive measurements of the cardiac output of the dye-dilution and the direct Fick methods, the correlation coefficient was 0.73, while in a smaller group the reproducibility of both methods was shown to be good.

The estimation of the so-called pulmonary blood volume is likewise a reproducible measurement. It appears that an anticipated error of $\pm$ 10 per cent renders the measurement insensitive to small but presumably significant changes in the pulmonary blood volume.

The constancy of the ratio of the pulmonary to the general blood volume under a variety of circumstances is rather remarkable and would appear to be evidence against the concept of the lung as a blood reservoir. The acute expansion or reduction of the effective blood volume does not alter the ratio of the general to the pulmonary blood volume. Pulmonary hypertension induced by hypoxia does not alter this ratio. The pulmonary blood volume and the ratio of the pulmonary to the general blood volume are normal in chronic pulmonary disease. It is only when the sharply contrasting hemodynamic abnormalities of tight mitral stenosis and free tricuspid insufficiency are compared that an equally significant difference in the ratio of the pulmonary to the general blood volume becomes apparent.

MINTZ

Lenègre, J., Scebat, L., Besson, H., Benchemoul, F., and Damien, J.: Pulmonary Capillary Pressure in Various Types of Heart Diseases. Arch. mal coeur **46:** 1 (Jan.), 1953.

A study of pulmonary "capillary" pressure was made by means of right heart catheterization in 134 cases. These included normal subjects and heart patients.

Normal pulmonary "capillary" pressure (pcp) was found between 3 and 10 cm. water, which is similar to left atrial pressure. Exertion or anxiety did not appreciably change this level of pressure.

Pulmonary "capillary" pressure was found elevated in every case where there was difficult emptying of the pulmonary veins—severe mitral stenosis, left ventricular failure, or constrictive pericarditis. In such cases, exertion or anxiety increased the level of pulmonary "capillary" pressure.

The highest level was found in acute pulmonary edema where the pressure was often above 47 cm. water. This level was then higher than that of colloidosmotic pressure of the blood.

Pulmonary "capillary" pressure is normal, even during exertion and in spite of severe pulmonic hypertension, both in chronic cor pulmonale and in congenital heart disease.

Measurement of pulmonary "capillary" pressure is of interest for the evaluation of the pulmonary effect of diseases of the left heart or constrictive pericarditis and for calculating the arteriocapillary gradient. This reveals the degree of pulmonary arteriolar resistance. An increase of this gradient is usually due to a pathologic process of an obstructive nature.

LUISADA

Osher, W. J.: Pressure-Flow Relationship of the Coronary System. Am. J. Physiol. **172:** 403 (Feb.), 1953.

When coronary pressure and flow were measured in the perfused dog heart the logarithm of one of these was a linear function of the other. This was true in both the beating and fibrillating heart. At any pressure value there was less flow in the fibrillating heart than in the normally beating heart at the same pressure.

OPPENHEIMER

German, W. J., and Black, S. P. W.: A Clinical and Experimental Determination of Pressure Within the Carotid Arteries. Yale J. Biol. & Med. **25:** 244 (Feb.), 1953.

About 75 per cent of intracranial aneurysms receive their major blood supply from the internal carotid arteries and can probably be favorably influenced by carotid ligation in the neck. The authors studied the dynamics within the internal carotid arteries under various conditions. Pressures were measured by means of an inductance-type gage. Intra-arterial pressure recordings from the common

carotid artery are sharply reduced by occlusion proximally; the remaining pressures represent collateral and reflux pressures from the external and internal carotids. Combined common and external carotid occlusion resulted in even sharper reductions in pressure. Pressure records are shown in a patient one year after common carotid ligation. They showed reductions of 45, 42, and 60 per cent in peak-pressure, mean pressure, and pulse pressure respectively. Arteriograms showed considerable reduction in the size of the patient's aneurysm. Data are presented from another case in which partial ligation of the common carotid was done. Pressure reductions were significant. From a theoretic consideration of the hydraulic forces acting upon an aneurysm, it is to be expected that proximal ligation has a sound basis.

ENSELBERG

Mixter, G., Jr.: Respiratory Augmentation of Inferior Vena Caval Flow Demonstrated by a Low-Resistance Phasic Flowmeter. Am. J. Physiol. **172:** 446 (Feb.), 1953.

The flowmeter used in these experiments combined Pitot and resistance principles. The experiments demonstrated that inspiration increases venous return to the heart from the inferior vena cava. Abdominal compression and thoracic suction are factors in this increase. Although they usually act together, either one may function separately.

OPPENHEIMER

Brecher, G. A., and Mixter, G., Jr.: Effect of Respiratory Movements on Superior Cava Flow Under Normal and Abnormal Conditions. Am. J. Physiol. **172:** 457 (Feb.), 1953.

During normal inspiration venous return to the heart was increased as extrathoracic veins emptied into intrathoracic vessels. When inspiration was deeper than normal, as in Müller's experiment, venous return was greater early in inspiration. Later in inspiration there is no further increase at a time when the extrathoracic veins are depleted and collapsed. However, flows were greater at the end of inspiration, even though there was partial peripheral collapse, than during the expiratory pause. Although there was a small reduction of flow during expiration, the over-all effect of respiratory movements was to produce a net increase of venous return when compared with the flow found during the absence of respiratory efforts. An increased blood volume enhanced the respiratory flow augmentation. Hypovolemia produced the opposite effect. Intermittent positive pressure respiration reduced superior vena cava return in the closed chest when compared with flows obtained during normal respiration.

OPPENHEIMER

Platts, M. M.: The Arterial Blood Gases in Pulmonary Heart Failure. Clin. Sc. **12:** 63 (Feb.), 1953.

Arterial blood gas analyses on four groups of pa-tients were found to be as follows: (1) Controls (no heart or lung disease), oxygen saturation, 93 to 99 per cent, carbon dioxide, 43 to 53 volumes per cent; (2) heart failure without pulmonary disease, oxygen saturation only slightly decreased, carbon dioxide normal; (3) pulmonary disease without heart failure, oxygen saturation over 72 per cent, carbon dioxide less than 60 volumes per cent; (4) pulmonary heart failure, oxygen saturation less than 72 per cent, carbon dioxide above 60 volumes per cent. When recovery from pulmonary heart failure occurred the oxygen rose above 72 per cent in all and the carbon dioxide fell below 60 in over half the cases.

In the absence of metabolic alkalosis, increased carbon dioxide and decreased oxygen in the arterial blood indicate a considerable defect in pulmonary ventilation. No such defect was found in the patients with nonpulmonary heart failure. However in chronic bronchitis and emphysema there is a variable defect in pulmonary ventilation which results in diminished oxygen and increased carbon dioxide tension. The latter is associated with a lowered ability to respond by hyperventilation to a further rise in carbon dioxide tension. Though successful treatment of pulmonary heart failure reversed these changes, arterial oxygen seldom rose above 88 per cent, which may represent the degree of permanent impairment of pulmonary ventilation in these patients. This impairment renders them liable to attacks of heart failure precipitated by recurrent pulmonary infections. In some of the patients whose carbon dioxide did not fall below 60 volumes per cent upon recovery from pulmonary heart failure, it is possible that some degree of metabolic alkalosis was present as a consequence of the use of mercurial diuretics. The latter, in causing diuresis, may result in a greater loss of chloride than sodium, with a concomitant rise in carbon dioxide.

ENSELBERG

Hetzel, P. S., Wood, E. H., and Burchell, H. B.: Pressure Pulses in the Right Side of the Heart in a Case of Amyloid Disease and in a Case of Idiopathic Heart Failure Simulating Constrictive Pericarditis. Proc. Staff Meet., Mayo Clin. **28:** 107 (Feb.), 1953.

Catheterization of the right side of the heart in a case of primary systemic amyloidosis and in a case of congestive heart failure of unknown origin revealed pulse contours similar to those known to occur in minor degree in some cases of heart failure, and considered, when very obvious, to be pathognomonic of constrictive pericarditis. The marked dip in the early diastolic pressure and subsequent high plateau level of the diastolic pressure in the ventricle are believed to be related to changes in diastolic filling and ventricular distensibility. This type of characteristic pressure tracing cannot be considered specific for constrictive pericarditis, since it has been found in other types of heart disease presum-

ably associated with alterations in the distensibility characteristics of the myocardium.

SIMON

Grossman, J., Weston, R. E., and Leiter, L.: A Method for Determining Cardiac Output by the Direct Fick Principle without Gas Analysis. J. Clin. Investigation **32:** 161 (Feb.), 1953.

The use of gas analysis in the Fick method of determination of cardiac output requires gaseous equilibrium between alveoli, blood, and tissues. Variations in respiratory function produced by anoxia, hyperventilation, exercise, etc., may lead to significant errors in the measured cardiac output. To overcome these difficulties a nongaseous test substance was suggested. This would have to produce a rapid, fairly constant, and easily measurable uptake and/or excretion of sufficient magnitude to produce a significant arteriovenous difference. Sodium paraaminohippurate (PAH) and its acetylated derivative, paraacetylaminohippuric acid (PACA) were studied. By this technic it is necessary to introduce a test substance into the lesser circulation distal to the point from which mixed venous blood is withdrawn. This was accomplished by placing the distal tip of a double lumen cardiac catheter into the pulmonary artery. The proximal lumen, used for withdrawal of mixed venous blood, was located 10 cm. back in the outflow tract of the right ventricle just below the pulmonic valve.

In a series of 18 patients, 11 of whom had congestive failure of varying degrees, the method was employed together with the usual oxygen technic and a good correlation was obtained. Further refinement and greater accuracy will apparently be readily achieved as the simpler operations involved in the chemical method provide a certain elasticity not present in the gas technic and require merely periodic withdrawal of arterial and mixed venous blood.

WAIFE

Price, H. L., Conner, E. H., and Dripps, R. D.: Concerning the Increase in Central Venous and Arterial Blood Pressures during Cyclopropane Anesthesia in Man. Anesthesiology **14:** 1 (Jan.), 1953.

The effects of cyclopropane anesthesia on central venous and brachial arterial blood pressure were studied in 15 hospitalized patients without cardiovascular or respiratory disease. The level of mean arterial blood pressure was elevated at surgical levels of cyclopropane anesthesia whether or not carbon dioxide accumulated in the blood. Arterial pressure, however, significantly increased in the presence of respiratory acidosis. A similar increase in central venous pressure was noted under the same conditions. The venous pressure elevation also occurred whether or not the arterial carbon dioxide tension increased, but a greater elevation was observed with an elevated carbon dioxide content. The increase in venous pressure was directly related to the cyclo-propane concentration in the blood and inversely related to the heart rate. A sharp rise in arterial pressure and a prompt fall in central venous pressure was observed when the cyclopropane concentration was reduced. The authors believe that the changes observed during cyclopropane anesthesia result primarily from a hemodynamic action of the drug itself and not directly from respiratory acidosis or anoxia, and suggest that cyclopropane might reduce the ability of the heart to eject blood while simultaneously increasing the return of peripheral blood to the heart.

SAGALL

Waser, P., and Himzenger, W.: Radiocirculographic Investigations of the Coronary Circulation Using Na²⁴ Cl. Cardiologia **22:** 65 (Fasc. 2), 1953.

For investigations of coronary flow in man, the authors used intravenous injection of sodium^{24} chloride into the right arm and subsequently measured the radioactivity over the heart. The radioactive solution flows first through the right and then through the left heart. Part of it then returns via the coronary system into the right chambers for a second circuit through the lungs and the heart. From the resulting peaks of the activity curve the coronary flow and its velocity can be determined. In 108 normal persons in supine position and with heart rates between 60 and 79, the coronary circulation time was 4.2 ± 0.18 second. With increasing heart rates and slight elevation of blood pressure, the coronary circulation time increased by 5.2 per cent, and the relative coronary flow (at a normal cardiac output) rose by 6.7 to 8.7 per cent.

The increase in coronary flow is partly related to the blood pressure elevation and partly to dilatation of the coronary bed. According to hemodynamic laws, both should lead to higher flow velocity and therefore to a decrease of the circulation time. Consequently, there must be some mechanism to account for the observed increase of the coronary circulation time at higher frequencies. This might possibly be effected by a decrease of coronary flow during diastole and a systolic reflux of blood into the aorta.

With augmentation of cardiac output the coronary bed is not only dilated but also possibly enlarged by the opening of additional and longer channels available for coronary circulation. An increase of coronary flow could also be demonstrated under the influence of anoxemia and certain drugs (aminophylline and nitroglycerin). Digitalis, however, remained without effect on coronary circulation.

PATHOLOGY

PICK

Edwards, J. E., Helmholz, H. F., DuShane, J. W., and Burchell, H. B.: Pathologic Study of Hearts Previously Catheterized. Proc. Staff Meet., Mayo Clin. **28:** 113 (Feb.), 1953.

Necropsy was performed on 28 patients who had undergone cardiac catheterization. One patient died during the cardiac catheterization, but necropsy did not show any lesions which could be attributed to the procedure. In only two cases could any traumatic cardiovascular lesions be demonstrated. In one there was a small focus of hemorrhage in the right atrium and in the other, there was fibrinous deposit on the intimal surface of the pulmonary trunk.

It could not be concluded in any case that pulmonary infarction followed the procedure of wedging the tip of the catheter in a small pulmonary artery for purposes of recording "pulmonary capillary pressure" and withdrawing blood samples therefrom. In five cases data are supplied to show how necropsy clarified unexplained conditions which had presented perplexing problems at the time of cardiac catheterization.

SIMON

Nordmann, M., Loeblich, H. J., and Koch, W.: The Pathology of Lymphatic Channels. I. General Principles of Lymph Flow and Resorption. Arch. Kreislaufforsch. **19:** 38 (Feb.), 1953.

The authors report direct observation on the circulation of lymph in the exposed mesentery of the small intestine of anesthetized rabbits. Spontaneous movements of the lymphatic vessels are minimal and consist of local constriction and some movement of lymphatic valves. Peristaltic waves were not observed. The principal function of the vessel wall appears to be maintenance of the intravascular pressure. The latter depends on the local pressure in neighboring blood vessels and tissues and is present even if blood flow in tissues surrounding a lymphatic channel is blocked by adrenaline.

The wall of lymphatic vessels responds by very slow contraction to mechanical, thermal, pharmacologic, and bacterial stimulation. This reaction is restricted to the area of stimulation but may reach considerable degrees and even result in temporary complete occlusion of the vessel. Acceleration of lymph flow occurs with increase of local blood and tissue pressure and/or decrease of lymph pressure. It is limited by the capacity of the draining lymph channels. Reversed lymph flow and return of lymph into the tissue occurs outside the lymph nodes only exceptionally and under extraordinary conditions.

PICK

De Loach, J. F., and Haynes, J. W.: Secondary Tumors of Heart and Pericardium. Arch. Int. Med. **91:** 224 (Feb.), 1953.

In a series of 2,547 consecutive autopsies performed at the Walter Reed Army Hospital during the past 11 years, a total of 980 cases of malignant disease were observed. The heart, including the pericardium, was the site of metastatic tumor in 137 cases, an incidence of 13.9 per cent. Carcinoma

of the lung invaded the heart and pericardium more frequently than did other malignant processes, with a rate of 21 per cent among 105 cases. Lymphatic leukemia invaded macroscopically in approximately the same percentage, but the case total was only sixty-two. An antemortem diagnosis was made in three cases in this series, one of which is reported in detail.

No simple explanation is advanced for the relatively high incidence of secondary involvement of the heart and pericardium in this series. Of possible significance is the fact that the patients were preponderantly young men. It is important that the physician interpret carefully cardiac signs and symptoms or electrocardiographic abnormalities in patients with malignant disease in order to avoid overlooking possible metastasis to the heart or pericardium. Antemortem diagnosis of such involvement may provide a more specific basis for ameliorative therapy.

BERNSTEIN

Copping, G. A.: Spontaneous Rupture of Abdominal Aorta. J.A.M.A. **151;** 374 (Jan. 31), 1953.

Forty cases of rupture of the abdominal aorta are presented. In all but two of these cases the abdominal aorta ruptured at the areas of aneurysmal dilatation, and in these two exceptions the perforation was through an area of atheromatous thinning. The rupture opening was usually linear, with an average length of 2.8 cm. and occurred somewhat oftener in the sides of the vessel than it did anteriorly or posteriorly. Surprisingly enough, the aneurysm occurred four times more frequently in the lower than in the upper abdominal portion of the aorta, and the rupture was a through-and-through tear rather than a burrowing or longitudinal dissecting process. In three-quarters of the cases the blood was extravasated entirely into the retroperitoneal region. It tracked somewhat oftener into the left flank although there were no greater number of left than of right-sided perforations. The average age of the total group was 65 with extremes of 31 and 88 years. In this series of cases the condition was diagnosed with certainty on only 11 occasions and in 14 other cases aortic hemorrhage was conidered in the differential diagnosis. Therefore, in almost half the cases the possibility of aortic hemorrhage was not even entertained. In the total group, no less than 35 separate clinical entities, none having any remote connection with aortic hemorrhage, were suggested as diagnoses.

KITCHELL

Bower, B. D., Gerrard, J., and MacGregor, M. E.: Acute Benign Pericarditis. A Report of Four Cases in Childhood. Brit. M. J. **1:** 244 (Jan. 31), 1953.

The authors describe four instances of acute benign pericarditis in children. There was one

relapse in one case. Aureomycin was thought by the authors to be beneficial although chloramphenicol was not. One of the cases occurred during an outbreak of epidemic myalgia. One of the other patients became ill within a week after a vague febrile illness in both parents. The authors suggest that acute benign pericarditis may be a complication or manifestation of Bornholm disease.

McKusick

Bowman, H. S.: Traumatic Rupture of the Heart with Intact Pericardium. Am. J. Clin. Path. **23:** 33 (Jan.), 1953.

A case of traumatic rupture of the normal heart with intact pericardium is reported, together with the autopsy findings. The mechanism of such cardiac rupture is explained by the indirect trauma creating a sudden rise in pressure in the cardiac cavity at a moment of full distension of that heart chamber, causing the organ to burst at a point of greatest strain.

Bernstein

PHARMACOLOGY

Moyer, J. H., and Mills, L. C.: Hexamethonium— Its Effect on Glomerular Filtration Rate, Maximal Tubular Function, and Renal Excretion of Electrolytes. J. Clin. Investigation **32;** 172 (Feb.), 1953.

Intravenous hexamethonium was administered to 14 control subjects and 22 patients with hypertension. With the reduction in blood pressure, there was an immediate reduction in glomerular filtration rate and sodium and water excretion. After one hour, despite a maintained reduction in pressure, the glomerular filtration returned to approximately control values. Sodium excretion increases in spite of a persistent antidiuretic effect. The initial effect on the kidney resembles that of a sympathetic renal nerve stimulation. Kidneys with marked impairment of function responded to hexamethonium hypotension in essentially the same way as in normal kidneys. This suggests that the nephrons are destroyed as anatomic units and the remaining nephrons function in a relatively normal fashion, not that they have a slower hemodynamic readjustment to a lowered blood pressure. Norepinephrine is an effective vasopressor agent after hexamethonium reduction of pressure. There was very little, if any, inhibition of potassium excretion.

The observations indicate that ganglionic blockade with hexamethonium is a dependable method for reducing blood pressure in both normotensive and hypertensive subjects. There was no associated reflex tachycardia, probably a result of the blockade of the sympathetics to the heart. Associated renal disease did not affect the blood pressure response, thus suggesting that even when kidneys are involved, autonomic nervous system imbalance plays a significant role in the development of hypertension.

Waife

Larson, R. K.: The Mechanism of Quinidine Purpura. Blood **8:** 16 (Jan.), 1953.

A case of thrombocytopenic purpura induced by quinidine was studied and evidence of a specific hypersensitivity mechanism was found. A rapid fall in circulating platelets occurred in the patient after a test dose of the drug. Inhibition of clot retraction could be produced in the patient's blood by the addition of minute quantities of quinidine in vitro. Complete inhibition of clot retraction could be produced in the blood of a normal individual by the addition of serum from the patient together with quinidine. No inhibition occurred if one or the other was added alone. It was felt that this was strong support for an antigen-antibody type of reaction.

Bernstein

Garb, S.: Effects of Epinephrine, Arterenol and Isuprel on the Electrical Potentials of Mammalian Heart Muscle: Inability of Nitrites to Block Effects. Am. J. Physiol. **172:** 399 (Feb.), 1953.

The test object in these experiments was the isolated cat papillary muscle. Contractile force and automaticity increased, the T wave became elevated, the R-T interval widened, and a U wave appeared under the influence of all three agents. These effects were not blocked by nitroglycerin or sodium nitrite.

Oppenheimer

Boxill, G. C., and Brown, R. V.: Epinephrine Prepotency over Pressoreceptor Responses Elicited by Elevated Blood Pressure. Am. J. Physiol. **172:** 385 (Feb.), 1953.

The authors question the ability of pressoreceptor reflexes to buffer or moderate hypertension in the presence of circulating epinephrine. This opinion is based on the experimental findings that full blocking doses of atropine and left cervical vagotomy do not change blood pressure level, peak pressure attained, extent of rise, or dose–response curves for increasing doses of epinephrine as compared to control animals. For high doses of epinephrine the duration of the pressure response is unchanged by the same experimental technics.

Oppenheimer

Mellman, E.: Clinical Studies on Veratrum Alkaloids. III. The Effect of Protoveratrine on Renal Function in Man. J. Clin. Investigation **32:** 80 (Jan.), 1953.

Using standard clearance technics, the renal function in 36 subjects was studied 43 times. After suitable control periods, clearances were measured for one and one-half hours after a single intravenous injection of protoveratrine, or for two hours after its intramuscular injection. It was found that with the acute onset of hypotension the effective renal plasma flow usually diminished about 8 per cent, but usually rose in one and one-half hours to control

levels or higher, although hypotension may have been maintained. The glomerular filtration rate fell more strikingly (about 22 per cent) with the onset of hypotension. After three hours of a persistent reduction in blood pressure the glomerular filtration rate averaged 16 per cent below control levels. Oliguria characteristically appeared with the lowering of blood pressure. Calculations show that renal vasodilatation occurred in patients with essential hypertension as well as in those with chronic glomerulonephritis when hypotension was maintained with protoveratrine. The major decrease in renal resistance occurred at the afferent glomerular arteriole.

WAIFE

Hall, C. E., and Hall, O.: The Potency of Certain Desoxycorticosterone Esters with Respect to the Production of Hypertension and Cardiovascular Lesions. Endocrinology **52:** 157 (Feb.), 1953.

The toxic effects of chronic treatment with desoxycorticosterone phenylacetate (DC-phenylacetate) and desoxycorticosterone trimethylacetate (DC-trimethylacetate) were compared with those of desoxycorticosterone acetate (DC-acetate), using unilaterally nephrectomized rats given 0.9 per cent sodium chloride as drinking water. The animals receiving desoxycorticosterone acetate and desoxycorticosterone phenylacetate showed a marked augmentation of fluid intake and a rapid onset of hypertension, edema and ascites. Although these same effects were seen in the rats receiving desoxycorticosterone trimethylacetate, they were milder, with a delayed onset. Renal enlargement was present to the same degree in all the treated groups, but cardiac hypertrophy, cardiovascular lesions such as arteriolar necrosis with perivascular infiltration of cells, glomerulosclerosis, and periarteritic type of lesions were more marked in the desoxycorticosterone acetate and desoxycorticosterone phenylacetate-treated groups than in the desoxycorticosterone trimethylacetate-treated group, probably because of the decreased incidence and severity of hypertension in the latter group.

CORTELL

Davis, J. O., and Howell, D. S.: Comparative Effect of ACTH, Cortisone and DCA on Renal Function, Electrolyte Excretion and Water Exchange in Normal Dogs. Endocrinology **52:** 245 (Feb.), 1953.

Corticotropin (ACTH), cortisone, and desoxycorticosterone acetate (DCA) were given successively for variable periods to four normal female dogs, and the effects on renal function, electrolyte metabolism, and water exchange studied. Glomerular filtration rate (GFR) and renal plasma flow (RPF) increased with all three hormones (except with corticotropin in one dog and desoxycorticosterone acetate in another). Water exchange was increased by all three hormones but there were quantitative and qualitative differences. The dia-

betes insipidus-like state produced by desoxycorticosterone acetate was dependent on a high sodium intake, whereas increased water turnover of lesser magnitude occurred with corticotropin and cortisone on both low and high sodium diets. The negative potassium balance which occurred during corticotropin and cortisone administration was probably a reflection of increased tissue catabolism since a concomitant loss of nitrogen occurred. The marked potassium depletion and the alkalosis which followed only when desoxycorticosterone acetate was given with a high sodium intake, resulted from a different mechanism, possibly related to a direct renal tubular effect.

The first one or two days of corticotropin and cortisone administration were accompanied by salt loss in three of the four dogs; since glomerular filtration rate was initially increased in these three but not in the fourth animal, there is a suggestive causal relationship between the elevated glomerular filtration rate and negative salt balance. Salt retention resulted during the corresponding period on desoxycorticosterone acetate. Thereafter, balance was maintained during administration of all three hormones in the presence of a high glomerular filtration rate, suggesting that increased tubular reabsorption of sodium and chloride were present. The sodium retaining effect of desoxycorticosterone acetate was greater than that of cortisone or adrenal cortical hormones released by corticotropin at the dosage levels employed. These studies demonstrate that the effect of corticotropin and cortisone on salt excretion in the dog differs from that reported for man.

CORTELL

Plavcic, C.: Therapeutic Application of an Extract of the Total Heart. Acta cardiol. **8:** 35 (Fasc. 1), 1953.

The authors report their experience with Recosen, an extract of the entire heart, in cases with heart failure, coronary disease, and various types of cardiac irregularities.

Recosen increases the tolerance to digitalis. Patients reacting to digitalis alone with symptoms and signs of toxicity can be given digitalis in combination with Recosen without ill effects, or can continue to use digitalis for more protracted periods. In two patients Recosen alleviated the signs of heart failure. In several cases of acute and chronic coronary insufficiency, Recosen injections were followed by improvement of symptoms and of electrocardiographic alterations. In cases of severe or irreversible heart failure, and in subacute bacterial endocarditis Recosen was without any therapeutic effect. No notable influence on cardiac rhythm was seen in cases of auricular flutter and fibrillation. The authors conclude that Recosen, if limited to certain indications, may be a useful supportive agent in the treatment of heart disease.

PICK

Haynes, F. W., Forsham, P. H., and Hume, D. M.: Effects of ACTH, Cortisone, Desoxycorticosterone, and Epinephrine on the Plasma Hypertensinogen and Renin Concentration of Dogs. Am. J. Physiol. 172: 265 (Feb.), 1953.

Corticotropin (ACTH), cortisone, and epinephrine increase plasma hypertensinogen. Unanesthetized dogs were the test objects and bioassay methods were used as criteria. Desoxycorticosterone and pituitrin produced no change. Rise in hypertensinogen levels lagged several hours behind beginning of injections, but remained high for several days after injections were stopped. Adrenalectomy prevented corticotropin effects. Desoxycorticoserone produced no detectable renin. It appeared occasionally in small amounts with corticotropin and cortisone. The authors postulate an increased production of hypertensinogen in the presence of 11–17 oxysteroids.

OPPENHEIMER

Schultz, A. L., Hammarsten, J. F., Heller, B. I., and Ebert, R. V.: A Critical Comparison of the T-1824 Dye and Iodinated Albumin Methods for Plasma Volume Measurements. J. Clin. Investigation. 32: 107 (Feb.), 1953.

One of the major criticisms of the T-1824 dye method for plasma volume determination has been that part of the dye is rapidly removed from plasma before binding with protein occurs. Since this does not apply to human serum albumin tagged with I^{131}, a comparison of the two methods was performed: Plasma volumes were determined simultaneously by the dye and iodinated albumin method in 28 subjects. The mean difference between the two was only 59 cc. and was not significant. The rapid intravenous administration of polyvinylpyrrolidone (PVP) resulted in an essentially similar increase in plasma volume determined by both methods. The cervical portion of the thoracic duct was cannulated in a man undergoing a neck dissection for localized lymphoblastoma. Studies with the iodinated albumin revealed that very little albumin appeared in the lymph during the first half hour after intravenous injection. The authors conclude that plasma volume measurements made with T-1824 dye are as valid and reliable as those made with the iodinated albumin technic.

WAIFE

Kvale, W. F.: Hexamethonium and Apresoline (1-Hydrazinophthalazine). Proc. Staff. Meet., Mayo Clin. 27: 489 (Nov.), 1952

The authors have been encouraged by the use of these drugs, particularly hexamethonium bromide, in selected cases of essential hypertension. Subcutaneous administration of hexamethonium bromide produces a hypotensive response in most cases, and in many cases it causes marked postural hypotension with all its secondary, unpleasant effects. These effects usually persist for three or four hours, but become less noticeable as the injections are continued, even though the dose may be increased.

Apresoline hydrochloride seems to cause a milder hypotensive effect than hexamethonium bromide, but in the reported cases the dosage was inadequate and the time too short to permit adequate evaluation. The usual side effects such as headache, palpitation, tremor, and anxiety can be diminished or abolished by the use of Pyribenzamine hydrochloride and phenobarbital. Because many untoward reactions can occur, and because of the need for injection of the hexamethonium bromide by the patient, two or three times daily, these drugs would seem to be indicated only in cases of severe hypertension.

SIMON

Hines, E. A., Jr.: Potassium Thiocyanate and Sodium Nitroprusside. Proc. Staff. Meet., Mayo Clin. 27: 485 (Nov.), 1952.

The effect of thiocyanates on the blood pressure of patients with hypertension still is not settled to the satisfaction of all investigators of this problem. Almost all who have studied the effects of thiocyanates in hypertensive disease agree that the majority of patients experience complete disappearance or considerable lessening of such symptoms as headache, vertigo, and nervous tension. The thiocyanates are not an effective treatment for hypertensive disease inasmuch as their effects are not due to any specific reversal of the vascular changes which produce the hypertension. The dosage of thiocyanates for the individual patient may be controlled easily and accurately by periodic determination of the level of cyanates in the blood. There are few or no other drugs for which we have as satisfactory a means by which the concentration of the drug in the patient may be controlled. Some contraindications to the use of thiocyanates are: (1) moderate or severe degrees of renal insufficiency, (2) arteriosclerosis of the central nervous system, (3) blood dyscrasias, (4) inability to obtain determinations of the level of thiocyanate in the blood at appropriate intervals. The type of patient for whom the use of thiocyanates is especially indicated is the relatively young patient with labile blood pressure who has severe migraine or headaches caused by hypertension.

The impression of the investigators who have studied the qualities of sodium nitroprusside is that although it has some of the properties of the thiocyanates, there is an additional effect which allows it to produce a quicker and more impressive hypotensive effect than does administration of the cyanates. Further investigation will be necessary before it can be determined whether or not use of sodium nitroprusside for patients with hypertension has any real advantages over use of thiocyanates as commonly administered.

SIMON

Droller, H.: Foliandrin in Geriatric Practice. Cardiologia **22:** 118 (Fasc. 2), 1953.

The author used Foliandrin, the active cardiac glycoside of leaves of nerium oleander, for treatment of congestive heart failure in a group of old patients with ischemic heart disease, and in a slightly younger group with chronic cor pulmonale. The usual initial dose was 0.4 mg. by mouth, followed by 0.2 mg. every eight hours until the pulse rate fell to 60 to 80 per minute. Thereafter the dose was adjusted individually. The results are described as very satisfactory and similar to those expected from any other potent digitalis preparation. Foliandrin acts quickly and is excreted rapidly with no or little cumulative action. Toxic symptoms were notably absent. Similar to digitalis it proved less effective in "high output failure" due to pulmonary emphysema, although there was some effect seen on the vital capacity. The poor results in cor pulmonale are ascribed to the fact that Foliandrin, like digitalis, lowers the right auricular pressure and hence, the filling pressure and output of the failing right ventricle.

PICK

Giarman, N. J., Mattie, L. R., and Stephenson, W. F.: Studies on the Antidiuretic Action of Morphine. Science **117:** 225 (Feb. 27), 1953.

It is well recognized that morphine has an antidiuretic action. In this study, antidiuretic hormone (ADH) assays were conducted in normal and hypophysectomized rats receiving morphine. Under the conditions of the experiment, hypophysectomized rats did not show the antidiuretic activity of morphine. Contrariwise, morphine consistently produced urine with distinct antidiuretic potency in these animals, although Demerol and methadone did not have a similar action. The authors believe that morphine stimulates the production of an antidiuretic substance by the neural hypophysis, and this substance has properties markedly similar to those reported for the antidiuretic hormone.

WAIFE

Livesay, W. R., and Chapman, D. W., The Treatment of Acute Hypotensive States with l-Norepinephrine. Am. J. M. Sc. **225:** 159 (Feb.), 1953.

The authors treated 22 patients in shock due to various causes including pulmonary embolism, myocardial infarction, hemorrhage, burns, hexamethonium administration, incompatible transfusion, arrythmia, and postoperative shock, with an intravenous infusion of 5 per cent glucose containing 4 mg. of 1:1000 norepinephrine. The rate of administration of the pressor agent was governed by the pressor response with blood pressure readings and pulse rates being determined at 5 to 15-minute intervals. In a few instances, the amount of norepinephrine was increased by 4 or 8 mg. when a satisfactory reaction failed to occur. In only two patients did the treatment fail to produce a pressor response; in one of these, ventricular fibrillation may have been produced by the drug. Of the six patients with myocardial infarction, five did not survive in spite of a satisfactory pressor effect in all but one patient. Seven patients were thought to have been saved by the treatment; 15 patients died despite treatment; four of these had a significant pressor effect but died later from other causes. In one patient the use of Benadryl together with norepinephrine was shown to have a significant potentiating effect upon the pressor response. Mention is also made of the potentiating pressor effects of the adrenal cortical steroids. It is suggested that an important factor in the shock syndrome is the decreased peripheral vascular tone of neurogenic origin. Norepinephrine is capable of producing a generalized vasoconstriction without exerting significant effects upon the heart. This should make it a suitable agent for combating shock.

SHUMAN

Millikan, C. H., Lundy, J. S., and Smith, L. A.: Evaluation of Stellate Ganglion Block for Acute Focal Cerebral Infarcts. J.A.M.A. **151:** 438 (Feb. 7), 1953.

Observations on 87 patients with focal cerebral vascular disease have been made. Twenty-seven of these patients had stellate ganglion block performed from a few minutes to six hours after the onset of symptoms of infarction. Sixty patients did not have stellate block. The two groups of patients are comparable from the standpoint of severity and extent of the lesion. Hemiplegia developed in 55 per cent of the patients receiving stellate ganglion block within 24 hours after onset of symptoms, and 51 per cent of the nonblock group had this neurologic sign in the same time period. Thirteen per cent of the group not receiving block were normal two weeks after the occurrence of infarction as contrasted with only 5 per cent of those receiving stellate block. Although the number of patients is inadequate for the development of conclusions, the claims of remarkable improvement of patients with focal cerebral disease when treated by stellate ganglion block has not been confirmed. Thus far the results of this treatment have not been better than those of a group of patients not receiving stellate ganglion block.

KITCHELL

Boniface, K. J., and Brown, J. M.: Quantitative Evaluation of Cardiovascular-Stimulant Drugs in Barbiturate Depression of the Heart of the Dog. Anesthesiology **14:** 23 (Jan.), 1953.

Sodium pentobarbital was administered to 35 dogs. The amount necessary to produce respiratory arrest and cardiac arrest employing artificial respira-

tion was determined. The cardiac arrest dose of sodium pentobarbital was considerably greater than the respiratory depressing dose. With artificial respiration and cardiovascular stimulants full recovery could be obtained after the administration of doses of pentobarbital approximately three times the usual respiratory dose. The relative extent in increasing the cardiac arrest dose level was determined for several cardiovascular stimulants. Previously administered ouabain increased the cardiac arrest dose by about 50 per cent. Ephedrine and Aranthol increased this level by about 200 per cent. Occasionally ephedrine produced cardiovascular depression not seen with Aranthol.

SAGALL

PHYSICAL SIGNS

Gunn, A. L., Wood, M. C.: The Amplification and Recording of Fetal Heart Sounds. Proc Roy. Soc. Med. **46**: 85 (Feb.), 1953.

The authors use a high gain amplifier that can detect a signal of less than 100 microvolts, and can amplify it several hundred thousand times without distortion, and at the same time retain a high signal-to-noise ratio. In the apparatus a crystal microphone converts the audible sounds into corresponding electrical impulses. The peak potential received from the microphone at term varies with the intensity of sound, from 200 to 500 microvolts.

The high impedance of the crystal microphone is matched by a cathode follower. The signal received is then amplified through two pentode stages which together form the preamplifier. The signal is tuned to whatever frequency is wanted and after further amplification may lead into any of several channels.

The recording of fetal heart sounds is not an easy procedure as the signal received from the microphone is small; and sounds from the abdomen, such as borborygmi, and skin noises have a frequency note that is in the same range as the fetal heart sounds and may cause interference. Mains hum and its harmonic also lie in this range and may be troublesome. The construction of a suitable amplifier necessitates adequate screening, and it is necessary to provide a well-stabilized power supply.

BERNSTEIN

Sloan, A. W., Wishart, M.: The Effect on the Human Third Heart Sound of Variations in the Rate of Filling of the Heart. Brit. Heart J. **15**: 25 (Jan.), 1953.

In 16 individuals, logarithmic phonocardiography showed that the third heart sound deflections are almost abolished by venous occlusion of the extremities with negligible changes in the deflections produced by the first and second heart sounds. After exercise, the third heart sound deflections were increased in 10 of 14 subjects and those of the first heart sound increased in all.

SOLOFF

PHYSIOLOGY

Perry, W. F., and Fyles, T. W.: Antidiuretic Activity of the Serum of Normal and Diseased Subjects. J. Clin. Endocrinol. & Metab. **13**: 64 (Jan.), 1953.

The antidiuretic activity of the serum of patients with cardiac edema and liver disease was studied by determining its effect on the water excretion of adult hydrated rats. An initial experiment demonstrated significant antidiuretic activity in the serum of dehydrated adult men compared with the serum of the same men following forced hydration. The antidiuretic activity of serum from a series of 10 patients with congestive heart failure did not differ significantly from the antidiuretic activity of the serum from a series of 13 normally hydrated subjects; there was a wide variation in results within each group. Nine patients showing liver damage of various etiologies, three cases of Addison's disease, and single cases of the nephrotic syndrome, lymphatic edema, Hodgkin's disease and lymphatic leukemia had sera whose antidiuretic activity fell within the normal range. These studies fail to demonstrate a relationship between the serum level of antidiuretic activity and water retention associated with congestive heart failure and liver disease.

CORTELL

Trautwein, W., and Zink, K.: Membrane and Action Potentials of Single Myocardial Fibres in the Warm Blooded Animal Heart in Situ. Verhandl. deutsch. Ges. Kreislaufforsch. **18**: 88, 1952.

The authors recorded with glass capillary electrodes of 0.5 to 1 μ diameter membrane and action potentials in single myocardial fibers of the exposed hearts of cats and dogs, and in excised Purkinje fibers.

In 33 successful measurements in the exposed hearts the membrane potential averaged 82 millivolts with a range of 76 to 96.5 millivolts. The action potential was in the average 102 millivolts, ranging from 96 to 114 millivolts. A distinct overshoot of depolarization was manifested by a sharp peak of the curve at the beginning of activation. The activation time was 0.6 millisecond. The duration of the action potentials varied with the rate of beating. When the heart was isolated and continued to beat in Tyrode solution, the values during the first two minutes of beating were similar to those of the heart in situ. With severe damage, and especially after the onset of fibrillation, the action potential became progressively smaller and eventually disappeared.

Membrane and action potentials recorded on excised Purkinje fibers were about 20 per cent higher than those recorded in ordinary myocardial fibers, but the time consumed for activation was less (0.3 to 0.5 millisecond).

PICK

Freinkel, N., Schreiner, G. E., and Athens, J. W.: Simultaneous Distribution of T-1824 and I¹³¹ Labeled Human Serum Albumin in Man. J. Clin. Investigation **32**: 138 (Feb.), 1953.

A stable bond forms between T-1824 and albumin in vitro. The rapidity of this union, its stability, and late metabolic fate have been studied in this experiment. Attention was directed to the very early and very late fate of the dye. The studies indicate that union of dye and protein in vivo is complete and virtually instantaneous, and that the disappearance of T-1824 thereafter approximates the actual exchange of albumin.

WAIFE

RHEUMATIC FEVER

Thomas, G. T., Besterman, E. M. M., and Hollman A.: Rheumatic Pericarditis. Brit. Heart J. **15**: 29 (Jan.), 1953.

The authors emphasize the differences in the clinical features and prognosis of rheumatic pericarditis with effusion from that of rheumatic dry pericarditis.

Dry pericarditis is a relatively unimportant early manifestation of active carditis. Pericarditis with effusion is a later and serious finding in active rheumatic fever. Fifteen of 30 of these individuals died. The later in the course of active rheumatic fever that effusion occurs, the more serious the prognosis. All but one who recovered had residual heart disease. Fever, tachypnea, pain, abnormal sedimentation rates, enlarged cardiac silhouettes, and abnormal electrocardiographic findings, particularly ST-T segment deviations, were frequently present.

SOLOFF

Bunim, J. J., Kuttner, A. G., Baldwin, J. S., and McEwen, C.: Cortisone and Corticotropin in Rheumatic Fever and Juvenile Rheumatoid Arthritis. J.A.M.A. **150**: 1273 (Nov. 29), 1952.

This report is based on an analysis made of 31 rheumatic fever cases (children) and 7 cases of juvenile rheumatoid arthritis. It appears that cortisone or corticotropin therapy produces striking and prompt clinical improvement in the extracardiac manifestations of acute rheumatic fever and suppresses both the systemic and articular manifestations in almost all cases of juvenile rheumatoid arthritis. The effects on the cardiac manifestations of rheumatic fever are more difficult to evaluate. At the present stage of knowledge it is not known whether the administration of adrenal cortical hormones results in the prevention or even significant diminution of damage to cardiac structures. It is clear that old inactive changes resulting from rheumatic heart disease are not reversed by hormone therapy. When administration of the hormones is discontinued in juvenile rheumatoid arthritis, relapses usually follow, and in some cases the pathologic processes of disease may advance even while

the clinical manifestations are suppressed. Adrenal cortical hormones are indicated especially in severe, rapidly progressing forms of disease where the patient is threatened with serious disability, invalidism or death. The administration of these agents must not, however, be the only therapeutic measure employed, but should constitute an integral part of the carefully planned, individualized, and comprehensive regimen of treatment.

KITCHELL

Kohn, K. H., Milzer, A., and MacLean, H.: Prophylaxis of Recurrences of Rheumatic Fever with Penicillin Given Orally. J.A.M.A. **151**: 347 (Jan. 31), 1953.

A five-year study of prophylaxis of recurrences of rheumatic fever with penicillin is described. Oral administration of 800,000 units of penicillin daily for seven consecutive days the first week of each month was shown to be effective in significantly reducing the number of recurrences for three successive rheumatic fever seasons. The results demonstrate the effectiveness of using such courses of penicillin rather than daily administration. It is relatively easy to remember such a program. It is less costly and it gives the patient a rest period from antibiotic effect. Bacteriologic results and the time of recurrences indicate that a routine monthly course supplemented by semimonthly courses in January, February, and March, in the Chicago area offered as effective a means of prophylaxis as any reported in the literature thus far. Routine year-round prophylaxis of recurrences of rheumatic fever with penicillin given orally is advocated.

KITCHELL

SURGERY IN HEART AND VASCULAR SYSTEM

Campbell, M., and Devchar, D.: Results of the Blalock-Taussig Operation in 200 Cases of Morbus Coeruleus. Brit. M. J. **1**: 3497 (Feb. 14), 1953.

A report is presented on results of 200 Blalock-Taussig operations performed up to the end of 1951, in cases of what the authors prefer to refer to merely as morbus coeruleus because of the not completely certain diagnosis in all instances. Four-fifths were less than 15 years of age. Only 8 per cent of the tetralogy of Fallot cases died, and 75 per cent attained great improvement. In the smaller group of more complex lesions, results were much less satisfactory with 30 per cent mortality and only 35 per cent improvement. Detailed comments on heart size, hematologic findings, cyanosis, clubbing, pulse pressure, and other features are made.

McKUSICK

Enticknap, J. B.: Biopsy of the Left Auricle in Mitral Stenosis. Brit. Heart J. **15**: 37 (Jan.), 1953.

The author examined 71 specimens of muscle from the left auricular appendages removed during

operations for mitral valvotomy. For control, he used myocardium removed during operations for pulmonic stenosis and auricles obtained at post mortem.

Intimal thickening of the diffuse and nodular form occurred in 32 per cent of the biopsy specimens. Incorporation of tissue derived from the organization of a thrombus accounted for some but not all of these findings. Cytoplasmic and nuclear changes in the cardiac muscle cells are interpreted as artefacts due to fixation. Cubing of endothelium is regarded as nonspecific.

Infiltrations resembling Aschoff cells were seen in about a third of the biopsies. The author believes that their minute structure is not typical of Aschoff bodies. Their endocardial distribution is also unusual. "Subclinical" rheumatic phenomena were not associated with these lesions.

For these reasons, the author prefers to regard these appearances as a new finding, the significance of which can be determined only by prolonged clinicopathologic investigation.

SOLOFF

Bailey, C. P., Redundo-Ramirez, H. P., and Larzeleke, H. B.: Surgical Treatment of Aortic Stenosis. J.A.M.A. **150:** 1647 (Dec. 27), 1952.

A series of 21 patients with severe aortic stenosis treated by simple dilatation is reported. Only one of these patients was treated with a retrograde passage (by the carotid approach) of the dilating instrument. Because that case ended in disaster the remainder of the cases were treated by the seemingly less attractive approach through the left ventricle by means of Donaldson's type of valve dilator. It was felt that incisional division, such as that used in congenital pulmonic valvular stenosis, is not satisfactory for treatment of acquired aortic stenosis. The inadvertent or intentional production of even a small degree of aortic regurgitation during an attempt at surgical relief of aortic stenosis is likely to end disastrously. This is because the thickened left ventricular wall and the nondilated ventricular chamber render the heart in these cases particularly unadaptable to compensate for a sudden surgical production of aortic regurgitation. The authors feel, however, that dilatation of the aortic valve can with reasonable safety be performed from below using the new dilator and its incorporated wire guide. When serious degrees of both aortic and mitral stenosis coexist, the authors precede the aortic dilatation by a mitral commissurotomy. In such cases, where only the mitral commissurotomy is performed, there may be an imbalance of the circulation with entrance of the blood into the left ventricle increased at the same time that obstruction to the ventricular outflow has remained. The authors feel that opening the valve to 50 per cent of the normal aperture is sufficient. The mortality in 11 patients where the valves were inadequately

dilated by an older form of instrument was eventually 36.2 per cent. There has been no mortality to the date of the article in nine patients adequately operated on by use of the new instrument.

KITCHELL

Pratt, G. H.: Angled Needle for Suturing Auricular Appendage in Commissurotomy. J.A.M.A. **151:** 127 (Jan. 10), 1953.

In the performance of a mitral commissurotomy the purse-string suture and over-sewing of the auricular appendage are of primary importance. Accidents or technical errors at this point not only are hazardous but may be fatal. Because of difficulties inherent with the old type needle, a new one has been developed. This is a ski type of needle, using atraumatic silk, with the base of the ski as a long square instead of a flat surface. This permits the needle to be held securely at any angle from 0 to 180 degrees. This also permits more satisfactory suturing in mitral commissurotomy.

KITCHELL

Glenn, W. W. L.: The Digital Exploration of the Ventricular Chambers of the Heart Through a Rubber Diverticulum. Yale J. Biol. & Med. **25:** 233 (Feb.), 1953.

In order to facilitate digital exploration within the ventricles, the author devised a method of using a closed rubber appendage, or diverticulum, which is temporarily attached to a ventricular wall. Through this device the wall can be incised and the finger inserted without blood loss. The technic is described and illustrated. The successful use of the method is reported in experiments on 26 dogs, in half of which the approach was employed to repair a previously made ventricular septal defect. It is suggested that this method of approach be considered in the human after further experimental experience.

ENSELBERG

Wolferth, C. C., Jeffers, W. A., Zintel, H. A., Hafkenschiel, J. H. and Hills, A. G.: Effects of Subtotal Adrenalectomy Alone and Combined with Sympathectomy upon the Blood Pressure Levels and Complications of Severe Arterial Hypertension. Bull. New York Acad. Med. **29:** 115 (Feb.), 1953.

This report deals with 56 cases of adrenalectomy for the treatment of severe, otherwise intractable arterial hypertension. The periods of postoperative observation ranged from 4 to 26 months. Failure to control hypertension will occur frequently if less than 95 per cent of the adrenal tissue is removed. Better control of blood pressure levels and more satisfactory clinical results are obtained by combining either abdominal sympathectomy with splanchnicectomy or thoracolumbar sympathectomy with subtotal adrenalectomy than are achieved by the

latter operation alone. Thirteen of the 56 patients subjected to adrenalectomy have died. An occasional death from a vascular accident at some time after operation appears to be unavoidable in patients with advanced vascular disease even though marked reduction of blood pressure is achieved.

The indications for adrenal cortical replacement therapy after adrenalectomy have been discussed. The possible sudden increase in requirements as a result of infection, gastrointestinal disturbance, extremely hot weather, or other forms of stress, must be kept in mind even in those who ordinarily require no replacement therapy. Subtotal adrenalectomy with or without sympathectomy has exhibited a remarkable beneficial effect upon nine cases of congestive heart failure complicating hypertensive disease. It is suggested that this improvement may be attributed in part to lowering of blood pressure and in part to altered regulation of electrolytes. The results of subtotal adrenalectomy with or without sympathectomy have been disappointing in hypertensives with advanced impairment of renal function. Marked improvement in so-called hypertensive retinopathy has been observed in the vast majority of patients. At least two, and possibly five, cerebral vascular accidents resulting in death have occurred at some time following operation. Two patients with advanced mental deterioration and retinopathy exhibited great improvement in mental acuity which seemed to parallel roughly improvement in the ocular fundi. The results obtained in this study have been encouraging enough to warrant continuance of investigation.

BERNSTEIN

Shumacker, H. B., Jr., and Lurie, P. R.: Pulmonary Valvulotomy. J. Thoracic Surg. **25**: 173 (Feb.), 1953.

The authors reported the results of valvulotomy in eight patients with pulmonary stenosis. No deaths occurred in the series, while good functional results were obtained in all instances. The procedure used to obtain exposure of the right ventricle and pulmonary artery was a midline sternal-splitting incision.

ABRAMSON

VASCULAR DISEASE

McDonald, L.: **Ischemic Heart Disease and Peripheral Occlusive Arterial Disease.** Brit. Heart J. **15**: 101 (Jan.), 1953.

Seventy-nine individuals presenting themselves with peripheral arterial occlusion and 50 with angina pectoris were studied with particular reference to the association of both disturbances in the same individual. Of the 79, 23 had angina pectoris and an additional 8 had abnormal electrocardiograms compatible with ischemic heart disease. Of the 50, 4 had intermittent claudication and an additional 8 had evidence of peripheral occlusive arterial disease.

SOLOFF

Campbell, E., and Burklund, C. W.: **Aneurysms of the Middle Cerebral Artery.** Ann. Surg. **137**: 18 (Jan.), 1953.

The authors described their experiences with excision of aneurysms of the middle cerebral artery in six patients. The various pitfalls associated with the surgical approach were stressed.

ABRAMSON

Palumbo, L. T., Quirin, L. F., and Conkling, R. W.: **Lumbar Sympathectomy for Peripheral Arteriosclerosis.** Ann. Surg. **137**: 61 (Jan.), 1953.

The authors presented their data following lumbar sympathectomy on 49 patients with arteriosclerosis obliterans. There was one postoperative death. The results were considered to be good in 43 patients and poor in six. One of the latter developed gangrene after operation.

It was concluded that in properly selected patients who have vasospasm and a vascular bed which is potentially elastic, improvement may follow sympathectomy. When a major amputation is necessary, it can most often be accomplished with safety at a lower level if preceded by such a procedure.

ABRAMSON

Dornhorst, A. C., and Whelan, R. F.: **The Blood Flow in Muscle Following Exercise and Circulatory Arrest: the Influence of Reduction in Effective Local Blood Pressure, of Arterial Hypoxia, and of Adrenaline.** Clin. Sc. **12**: 33 (Feb.), 1953.

Blood flow through the calf was studied by venous occlusion plethysmography in normal limbs following standard exercise and local circulatory arrest, as well as during arterial hypoxia. The authors found that the period of reactive hyperemia was not prolonged following reduction of effective local arterial pressure by 50 per cent. Arterial hypoxia produced by breathing 8 per cent oxygen had little effect on either postexercise or postischemic hyperemia. No quantitative debt-payment relationship was found. Adrenaline had little effect on postexercise response, but it did prolong the postischemic hyperemia, possibly by decreasing capillary permeability to diffusing metabolites.

ENSELBERG

Palumbo, L. T., Quirin, L. F., and Conkling, R. W: **Lumbar Sympathectomy in the Treatment of Peripheral Vascular Diseases.** Surg., Gynec. & Obst. **96**: 162 (Feb.), 1953.

The authors studied the effect of lumbar sympathectomy on 159 patients with various types of peripheral vascular disorders. Of this number, 49 suffered from arteriosclerosis obliterans. Postoperative complications occurred in 11 of these and consisted of a cerebrovascular accident, embolus to the leg, pulmonary embolism, neuritis of the anterior portion of the thigh, and paralytic ileus. The postoperative evaluation indicated that the results were excellent in 7, good in 23, fair in 13, and poor in 6 patients. Of

the 31 cases of thromboangiitis obliterans, the results were considered to be excellent in 14, good in 14, fair in 2, and poor in one.

The remaining patients in the series were suffering either from arterial embolism, frostbite, immersion foot, causalgia, or chronic thrombophlebitis. The poorest results were obtained in the patients with chronic phlebitis, who manifested edema, chronic cellulitis, ulcers, and pain.

It was concluded that lumbar sympathectomy is indicated in vascular cases demonstrating a vaso-spastic element and an elastic potentiality of the peripheral bed. It may also prevent or delay the need for a major amputation in many cases.

ABRAMSON

Malinow, M. R., Hojman, D., and Pellegrino, A. A.: Experimental Generalized Atherosclerosis in the Rat. Ciencia e Investig. **9:** 39, 1953.

Rats were subjected to unilateral or bilateral cellophane perinephritis and then rendered hypo-thyroid through methylthiouracil feeding. Choles-terol in oil (4 cc. of a 25 per cent solution) was then given daily with a gastric catheter. After 66 days of such a regimen, typical lesions of atherosclerosis, including intimal proliferation, foam cell formation, cholesterol deposits, and necrosis of the proliferated zone, were found in medium sized, muscular arteries (carotids, coronaries, renals, intercostals, etc.).

AUTHORS

Schmidt, J.: The Arteria Lusoria. Arch. Kreislauf-forsch. **19:** 1 (Feb.), 1953.

Based on eight of his own observations and a re-view of the literature, the author describes various types of arteries which, due to an anomalous origin from the aorta, cross the esophagus and produce the clinical symptom of dysphagia lusoria. Em-bryologically, all these vessels are derived from a preformed vascular ring containing the pair of the fourth branchial arches, each of which gives off an ascending and descending aorta. A number of de-velopmental anomalies is possible with respect to the origin, the caliber, and the course of arteries which eventually originate from the remaining aortic arch. This may also involve a vertebral artery, the common carotid artery or the innominate artery.

The main diagnostic signs of an arteria lusoria are found at x-ray examination and consist of the demonstration of a "lusoria band" and a "lusoria bed." The lusoria band is a string-like filling defect of the esophagus running in an upwards direction. The lusoria bed is an unusual impression of the dorsolateral aspect of the esophagus, just above the level of the aortic arch. It contains a soft pulsating shadow and is best seen when the patient is rotated and slightly bent to his right. Other symptoms, mainly due to compression of various mediastinal organs by the anomalous vessel, are discussed in detail.

In any case of dysphagia the presence of an arteria lusoria should be ruled out roentgenologically before the introduction into the esophagus of nonflexible instruments or solid dilating sounds. The primary interest of the vascular anomaly lies with the surgeon since in many cases it is amenable to an operation. The various methods used for surgery are described.

PICK

Doane, J. C., Paul, A. J., and Sohn, W. J.: Perfora-tion of Major Vein with Polyethylene Tubing. J.A.M.A. **151:** 384 (Jan. 31), 1953.

This article is a warning on the danger of vein perforation when using polyethylene tubing for prolonged intravenous administration of fluids. The authors feel such an occurrence is a possibility where the veins are excessively friable, where the tube used has an excessively large caliber, or where there is a sharp bevel at the tip of the tube.

KITCHELL

Randall, J. E., and Horvath, S. M.: Relationship between Duration of Ischemia and Reactive Hy-peremia in a Single Vessel. Am. J. Physiol. **172:** 391 (Feb.), 1953.

The amount of reactive hyperemia obtained in these experiments was least when there was a normal collateral circulation. Blood flow during hyperemia did not increase for occlusion periods longer than one minute. The maximum increase in flow during hy-peremia was 67 per cent. Hyperemia did not last longer than 45 seconds after occlusions up to five minutes. Where collateral circulation was least as in a leg, flow during hyperemia repaid only 60 per cent of blood flow debt accumulated during an oc-clusion of 10 seconds. If the occlusion was longer, the debt repaid was still less.

OPPENHEIMER

Naide, M.: Relation of Growth of Hair on Digits to the Severity of Ischemia. New England J. Med. **248:** 179 (Jan. 29), 1953.

The author studied the rate of growth of hair on toes with an impaired arterial circulation, in an at-tempt to determine whether any correlation could be made between this factor and the future viability of the lower extremity. In the presence of very severe ischemia, no hair was found on the toes, while with mild or moderate involvement, hair growth was normal.

It was the author's belief that the factor of hair growth was of value in deciding upon the therapeutic program for patients with gangrene. He noted that when good hair growth was present on toes with necrotic lesions, conservative treatment generally resulted in healing. On the other hand, absence of hair indicated that amputation would eventually have to be performed.

ABRAMSON

OTHER SUBJECTS

Allan, T. H., and Gregersen, M. I.: Measurement of Plasma Volume in the Dog with High Concentrations of T-1824. Am. J. Physiol. **172**: 377 (Feb.), 1953.

It was demonstrated in these experiments that the volume distribution of T-1824 is independent of concentration up to 1.3 mg. per milliliter. Above this concentration hemolysis is produced in dog's blood. The amount of hemolysis was shown to vary with predicted concentrations of free dye. Human erythrocytes were not hemolyzed by T-1824 even though dye concentrations were raised to 5 mg. per milliliter. The authors state that in dogs' blood, toxic effects of massive injections may be related to the hemolytic action of high concentrations of free dye.

OPPENHEIMER

Keating, D. R., Burkey, J. N., Hellerstein, H. R., and Feil, H.: Chronic Massive Thrombosis of Pulmonary Arteries. A Report of Seven Cases with Clinical and Necropsy Studies. Am. J. Roentgenol. **69**: 208 (Feb.), 1953.

The authors present the clinical, electrocardiographic, roentgenographic and pathologic findings in seven cases of chronic massive thrombosis of major pulmonary arteries. The findings indicate that this clinical entity is characterized by chronic congestive heart failure (duration, two months to four years), *without* passive congestion of the lungs; enlarged pulmonary arteries proximal to the point of obstruction; increased radiolucency of the lung fields as the result of ischemia; electrocardiographic findings of right ventricular hypertrophy or a shift from left to right axis deviation; clubbing and cyanosis; inconstant murmurs (three of the seven cases had diastolic murmurs); and a subacute or chronic course suddenly terminating in death.

SCHWEDEL

Swan, H. J. C., and Wood, E. H.: Localization of Cardiac Defects by Dye-Dilution Curves Recorded After Injection of T-1824 at Multiple Sites in the Heart and Great Vessels during Cardiac Catheterization. Proc. Staff Meet., Mayo Clin. **28**: 95 (Feb.), 1953.

The purpose of this paper is to further amplify the diagnostic uses of dye-dilution curves made possible by the injection of dye at various sites in the heart and great vessels during cardiac catheterization. In the control group, the dilution curves seen after central injection of dye differ from those after peripheral injection in that the time components in the former curves were reduced in comparison with the latter, while the concentration components were accentuated. This was not so in the patients who had cyanotic heart disease. Depending on the type of defect present, radical alterations in the contour of the curves were observed after injection of dye into different sites in the heart and great vessels.

If a right-to-left shunt is present, injection of dye in a chamber beyond the defect results in a curve of essentially normal contour. If, however, the injection is made at, or proximal to, the site of the defect a curve characteristic of that associated with right-to-left shunt is obtained. The differentiation of right-to-left shunts that occurs through an atrial septal defect, a ventricular septal defect, or a patent ductus arteriosus has been made possible by the use of this technic. It is possible, by a comparison of the magnitude of certain portions of the curves, to estimate the proportion of blood that traverses each route.

SIMON

Stone, D. J., Schwartz, A., Newman, W., Feltman, J. A., and Lovelock, F. J.: Precipitation by Pulmonary Infection of Acute Anoxia, Cardiac Failure, and Respiratory Acidosis in Chronic Pulmonary Disease. Am. J. Med. **14**: 14 (Jan.), 1953.

This practical study illustrates how infection led to acute anoxia, respiratory acidosis, and cardiac failure in four patients with chronic pulmonary disease. The authors show by physiologic studies the danger of oxygen therapy without some form of artificial respiration and present a therapeutic program which has as its objectives relief of anoxia, control of infection, and avoidance of decompensated respiratory acidosis. Since infection with excessive secretion and possibly accompanying bronchial spasm is the major factor in diminishing the airway, control of the infection with adequate antibiotic therapy, particularly penicillin, is of primary importance at the onset. The use of bronchodilators, such as aerosol epinephrine, is helpful. There is no question, in view of the cyanosis, that oxygen therapy is necessary. This should be instituted immediately with extreme care taken to observe the patient's ventilation and mental responses. If there is noted increasing mental stupor or confusion, a decrease in ventilation, a significant increase in arterial carbon dioxide pressure, or a decrease in pH while the patient receives the oxygen, artificial respiration is indicated immediately. Digitalis should be employed when indicated in the treatment of these patients. Of clinical interest was the absence of fever and leukocytosis in some of these patients. Cardiac failure was observed for the first time in these patients following the infection. There was usually evidence of right heart strain and pulmonary artery hypertension.

HARRIS

Perkins, R. B., and Bradshaw, H. H.: Pulmonary Infarction Mistaken for Bronchogenic Carcinoma. J.A.M.A. **151**: 545 (Feb. 14), 1953.

Two cases of pulmonary infarction which were subjected to thoracotomy because they had an

atypical roentgen picture are reported. It is pointed out that from the roentgenographic standpoint infarction may mimic almost any other lung disease. Prior to exploration of the suspicious lung lesion deliberate consideration should be given to the diagnosis of infarct. In the handling of a routine unexplained silent lung lesion, history and physical examination should routinely include attention to the lower extremities, the heart and other sources of emboli. The roentgenogram should be critically reviewed and increased use of angiocardiography should prove effective in making the diagnosis clearer in many cases.

KITCHELL

McDonald, E. L., and Palmer, K. N. V. (for Kekwick, A.): Edema Due to Subacute Nephritis Treated with Ion-exchange Resins. Proc. Roy. Soc. Med. 46: 46 (Jan.), 1953.

An ion-exchange resin of the mixed cation and anion type proved useful in the relief of renal edema in a a patient who had failed to respond to other measures.

BERNSTEIN

Coventry, M. B.: Problem of Painful Shoulder. J.A.M.A. 151: 177 (Jan. 17), 1953.

The author recognizes three forms of periarthritis of the shoulder: (1) pain with minimal stiffness, (2) "frozen" shoulder, and (3) the shoulder-hand syndrome. There are many causes for painful shoulder, but the occurrence of periarthritis is dependent on disuse and the presence of a periarthritic personality. The author feels that the initial cause of periarthritis is pain, but two other factors—disuse and a peculiar constitutional and emotional state, which he terms the periarthritic personality—are needed to produce a definite syndrome. Recovery is directly related to use of the shoulder. The sensitivity of the sympathetic nerves to disease may be peculiar to the periarthritic personality, and reflex sympathetic dystrophy is the probable cause of stiffness and other changes in the shoulder and hand in periarthritis. Treatment is directed towards reversal of the disuse syndrome and any means that can be given the patient to induce use of the shoulder will result in recovery. The author has found that cortisone is one of the most helpful stimuli.

KITCHELL

Hurwitt, E., and Seidenberg, B.: Rupture of the Heart during Cardiac Massage. Ann. Surg. 137: 115 (Jan.), 1953.

A case is described of a female patient in whom asystole of the heart occurred during an operation for the removal of an embolus at the aortic bifurcation. Cardiac massage was instituted after arrest had been present for two or three minutes, and oxygenation was maintained by controlled respiration. When two minutes of massage produced no effect, 4 cc. of 10 per cent calcium chloride was injected into the cavity of the left ventricle. Shortly thereafter a spontaneous cardiac beat was detected, but this was followed by the appearance of a pool of dark blood arising from the heart. It was then found that the thumb of the operator had penetrated the right ventricle through an area of softening in the anterior wall. Despite attempts to sew up the opening, the patient died.

ABRAMSON

Feitelberg, S., Nabatoff, R. A., and Touroff, A. S. W.: An Apparatus to Measure Elasticity of Blood Vessels. Ann. Surg. 137: 141 (Jan.), 1953.

An instrument is described which measures the elasticity of vessel grafts. It consists of a spring balance and a cathetometer, the former exerting tension on the vessel and the latter measuring the changes in length. The instrument is so designed that during the determination the tissues can remain immersed in a beaker containing normal saline solution.

By plotting the increase in force against the changes in length per unit of graft, the elasticity curve of the vessel can be obtained accurately.

ABRAMSON

Baggenstoss, A. H.: Visceral Lesions in Disseminated Lupus Erythematosus. Proc. Staff. Meet., Mayo Clinic 27: 412 (Oct.), 1952.

Acute disseminated lupus erythematosus is a systemic disease in which anatomic lesions are found predominantly in the kidneys, heart, spleen, and limbs. Any organ, however, may be involved, particularly in its vascular or supporting components. Diffuse or focal fibrinous pericarditis occurs frequently. It may be recent, organizing, or healed. If healing has occurred, the pericardial sac may be obliterated by fibrous adhesions. The process may extend beyond the pericardium to the pleura and bind the two serous surfaces together. The only distinctive lesion when it is present has been called "fibrinoid degeneration of the interstitial ground substance and collagen fibers." The endocardium is the site of a nonbacterial, verrucous endocarditis in about 40 per cent of cases. They may be single or conglomerate. They are seen on both sides of the heart with equal frequency.

The myocardial lesions reveal fibrinoid degeneration of interstitial collagen fibers usually associated with a moderate exudative reaction. The prominent fibrinoid degeneration and exudative reaction are in distinct contrast to the lesions observed in rheumatic fever, in which the alterative changes (fibrinoid degeneration) are difficult to find and proliferative phenomena are predominant over the exudative reaction. Although the appearance of many of the lesions of lupus erythematosus resembles hyperergic or allergic inflammatory reactions, one is not justified, on the basis of morphologic evidence alone,

in considering lupus erythematosus as a manifestation of hypersensitivity.

<div align="right">SIMON</div>

Burchell, H. B., Helmholz, H. F., and Wood, E. H.: Over-all Experiences with Cardiac Catheterization. Proc. Staff. Meet., Mayo Clinic **28**: 50 (Feb.), 1953.

In only a very small minority of cardiac patients is cardiac catheterization needed. The patients with pulmonary hypertension constitute a special group. In such patients the hypertension may be related to extensive pulmonary disease, to previous pulmonary embolism, to an undiagnosed congenital cardiac defect, or, in some instances, to pulmonary arteriolar disease. The diagnosis of idiopathic pulmonary hypertension is not always easily made, as at the time of the catheterization an intracardiac shunt may be so minimal that a cardiac defect might remain unrecognized. In two cases in this group, postmortem examination did not disclose any etiologic basis for the initiation of the pulmonary hypertension found. Of interest are some unusual cases. The diagnosis of Ebstein's malformation was made four times, anomalous pulmonary veins five times, tricuspid atresia four times, ruptured aneurysm of the sinus of Valsalva three times, and persistent atrioventricular canal three times. In the cases in which aneurysm of the aortic sinus was diagnosed, the evidence indicated that the site of rupture of the aneurysm communicated with the right ventricle in two cases and with the right atrium in one case. The diagnosis rested on the history and the presence of a loud continuous bruit, as well as on the catheterization findings in two cases and on postmortem findings in the other case in which there was an associated ventricular septal defect.

In the group of cyanotic congenital cardiac patients, the procedure is usually aimed at determination of the pulmonary arterial pressure or the nature of the pulmonary stenosis, if such exists. The use of multiple injections of dye via the cardiac catheter to determine the site of the venous arterial shunt, has added tremendously to the value of the catheterization procedure in this group of patients. In the group of acyanotic congenital cardiac patients, the catheterization procedure usually reveals the definite diagnosis, on the basis of the site of increased oxygen saturation in the right heart, but it is evident that the data must be correlated with the clinical findings. For instance, a ruptured aneurysm of the sinus of Valsalva might be interpreted as a ventricular septal defect from the cardiac catheterization data alone, or a persistent atrioventricular canal as an atrial septal defect. The majority of patients having a patent ductus arteriosus do not require special study, and only when patients with ventricular or atrial septal defects have atypical findings or are being categorized for future surgical therapy is cardiac catheterization carried out. In patients with constrictive pericarditis, the findings have indicated that either the right or the left ventricle may be the more significantly compromised. In the majority, pulmonary hypertension is found.

The following complications have been encountered. Transient arrhythmias, particularly ventricular extrasystoles, are so common as to be expected though not disregarded. The catheterization procedure is considered to entail a real risk, and as an index of this concern, a plan for cardiac resuscitation by the direct approach and cardiac massage has been rehearsed by the catheterization team. The continuous monitoring by the electrocardiogram, the pressure at the tip of the catheter and the arterial saturation as determined by the ear oximeter during the procedure are considered safety measures. Local thrombosis of the arm veins of minor degree is frequent; it was noted to be sufficiently extensive to involve the axillary veins in six instances, but in these it was without permanent sequelae.

<div align="right">SIMON</div>

BOOK REVIEWS

Cardiopatia Beriberica. *A. Burlamaqui Benchimol*
Postgraduate thesis. Rio de Janeiro, Gráficos
Bloch S. A., 1952. 218 pages, 87 figures.

This monograph is based on the clinical study of
30 cases of beriberi heart disease observed in the city
of Rio de Janerio and followed for periods varying
from several weeks to three years. The author
believes that oriental and occidental beriberi are
varieties of a basically similar condition. In the
Western Hemisphere those developing the disease
are usually chronic alcoholics. While one-half of the
patients had an inadequate diet, the others were
well nourished and even obese.

Peripheral edema was a prominent and early
sign; dyspnea was common and occasionally iso-
lated. Heart failure usually manifested itself with
the picture of left ventricular failure and was at
times accompanied by hypertension. Rapid circula-
tion time was present in 50 per cent of the patients.
Out of three cases with an acute type of failure
(Shoshin), two recovered after thiamin therapy.
All cases presented x-ray evidence of cardiac en-
largement usually with most severe enlargement of
the left ventricle. The heart size returned to normal
in 12 cases following therapy, while it was still
somewhat enlarged in the others. Incomplete return
to normal size is attributed to irreversible myo-
cardial damage. Fifteen cases had electrocardio-
graphic evidence of left ventricular enlargement;
threehad right bundle branch block; one, left bundle
branch block. Occurrence of accentuation of in-
verted T waves was noted during clinical recovery.
The clinical signs of diagnostic importance and the
laboratory data are reviewed by the author. Many of
the described tests were found valueless, including
the adrenaline and pitressin tests; the others were
frequently found unnecessary because the diagnosis
was made on clinical and therapeutic data.

This monograph is well documented. It represents
an important contribution to the study of beriberi
heart disease in our hemisphere and to the therapy
of chronic alcoholism.

A. A. LUISADA

**The Low Sodium Cook Book. How to Prepare
Tasteful Meals for the Low Sodium or Low Salt
Diet—Including Suggestions for the Low Sodium,
Low Fat, Low Cholesterol Diet.** *Alma Smith
Payne, M.A., and Dorothy Callahan, B.S. Intro-
duction by Francis L. Chamberlain, M.D., M.Sc.D.*
Boston, Little, Brown, 1953. 477 pages, 6 tables.
$4.00.

In this handbook of low sodium eating, the authors
begin by stressing the fact that a complete change
in eating habits is to be undertaken when a low
sodium diet is prescribed by the physician. With this
in mind, they build a new system of eating habits
for the restricted patient. The sodium count method
is stressed for the daily routine eating which is
eventually, with practice, the easiest way of guard-
ing one's self against infractions in diet. Daily menus
are given along with many recipes for common and
special dishes. The use of herbs and other low sodium
flavoring agents is stressed and described in detail.
Commercial preparations are described and re-
stricted items also stressed. A worthwhile appendix
appears listing approximately 600 foods and their
sodium content as well as the sodium content of
drinking water in over 100 cities throughout the
United States.

The authors have done an excellent job of pre-
paring a guide which should open new vistas for the
gourmet restricted in his salt intake and should be
of great help to the physician in this realm of treat-
ment.

D. J. RINEHART

**French Bibliographical Digest. Medicine: Heart and
Blood Vessels.** *Published and Edited by The Cul-
tural Division of the French Embassy,* New York,
1952, 127 pages.

The purpose and scope of this publication is stated
in the foreword which was written by André Cour-
nand, M.D.

"The Cultural Division of the French Embassy
is presenting the first of its French bibliographical
digests in Medicine. In this volume, which deals
with the Heart and Blood Vessels, will be found over
500 references, including books published since 1945,
those published during the year 1950 and 1951, and
articles which appeared in various French periodi-
cals in 1951. Professor Leriche, whose name and
pioneer work is well known to the American medical
public, has written an introductory article, in which
he analyzes, and summarizes, some of the most
significant developments in the study of cardio-
vascular diseases, particularly in the field of cardiac
and vascular surgery. Together with the long index
of publications, this article bears witness to the
remarkable vitality of French clinicians, surgeons
and investigators. It is my hope that this booklet,
and the others to follow, will encourage American
physicians and surgeons to look for the listed books
and articles to be found on the shelves of their well-
stocked library, to read them and thus to familiarize
themselves with the current French medical litera-
ture."

AMERICAN HEART ASSOCIATION, INC.

SECOND WORLD CONGRESS OF CARDI-OLOGY AND TWENTY-SEVENTH SCIENTIFIC SESSIONS OF AMERICAN HEART ASSOCIATION

September 12–17, 1954

The Organization Committee of the Congress and the Board of Directors of the American Heart Association have decided to combine the Congress and the Twenty-Seventh Scientific Sessions of the Association, scheduled for Washington, D. C., next September. The Scientific Sessions originally were to be held separately, immediately following the Congress. The official title of the Congress, previously referred to as the Second International Congress of Cardiology, is the Second World Congress of Cardiology.

The scientific sessions and exhibits will be located at the National Guard Armory in Washington, D. C. *The joint scientific program will be held Monday, September 13, through Friday, September 17. Opening Ceremonies* will be held on Sunday morning, September 12, in Constitution Hall. Plans include a reception on Sunday afternoon at the Mayflower Hotel. A joint banquet has been scheduled for Tuesday evening, September 14, at the Mayflower and Statler Hotels. An evening of entertainment has been set for Thursday, September 16. Conducted tours are being planned through the National Institutes of Health and the Navy medical center at Bethesda, Md., and the Army medical center.

Registration will take place at the Mayflower Hotel and the National Guard Armory.

Membership will be open to all members of affiliated national cardiological societies and associations throughout the world, and to physicians and other scientists who are interested in the field of cardiology and the circulation.

Abstracts. Those desiring to present papers must submit titles and abstracts of *not over 200 words* in English, and may additionally submit abstracts in one of three foreign languages—French, Spanish or German. Both abstracts and translations must be submitted in duplicate, typed double-spaced with wide margins, and on one side of the sheet only. Abstracts should be sent to the Secretaries of the respective national cardiological societies. These officers will forward to the Secretary General only those papers which have been approved by the executive committee of each national society.

United States and Canadian scientists will submit abstracts to the Medical Director of the American Heart Association for evaluation by the Program Committee of the Association.

From countries where there are no cardiological societies, titles and abstracts should be sent to the following:

In Europe: To Dr. F. Van Dooren, Secretary-General, Pan European Cardiological Society, 800 rue Mercelis, Brussels, Belgium.

In Latin America: To Professor Ignacio Chavez, Director, National Institute of Cardiology, Mexico City, Mexico.

In other areas: To Dr. L. W. Gorham, Secretary-General, Second World Congress of Cardiology, 44 East 23rd Street, New York 10. N. Y.

The final program will be decided upon by the Program Committee of the Congress in consultation with the Program Committee of the Association.

Abstracts from countries other than the United States must be received at the National Office of the Association, 44 East 23rd Street, New York 10, N. Y., *on or before March 1, 1954.* Abstracts from the United States and Canada must be received *by April 1, 1954.*

Registration fees: Members, $25.00, includes entry to the scientific sessions and exhibits, a Congressional badge, the printed program

containing abstracts, and attendance at the official banquet and other social events.

Associate members, $15.00—for wives and families. Includes all of the above privileges except program and badge.

For limited attendance (includes scientific sessions and exhibits only): for physicians, $10.00; for medical students, interns, residents, nurses, and other guests, $5.00.

Fees are payable in advance in dollars by money order or by draft on a United States bank.

SCIENTIFIC PROGRAM OF SECTION ON CLINICAL CARDIOLOGY

The Section on Clinical Cardiology of the American Heart Association will sponsor a two-day scientific program at the Conrad Hilton Hotel in Chicago on April 3 and 4, 1954. This program will follow the Annual Meeting of the Assembly of the American Heart Association and will immediately precede the Annual Sessions of the American College of Physicians. The meeting will be open to all members of the medical profession. Wright R. Adams, M.D., Chicago, is Chairman of the Program Committee. Any member of the American Heart Association who wishes to present a paper should send a 250 to 300 word abstract of the proposed paper to Charles D. Marple, M.D., Medical Director, American Heart Association, 44 East 23rd Street, New York 10, N. Y. All papers should be on the subjects of distinct clinical interest. *The deadline for the receipt of abstracts is Jan. 1, 1954.*

SECOND SOUTH AMERICAN CONGRESS OF ANGIOLOGY

The Brazilian Society of Angiology, affiliated with the South American Chapter of the International Society of Angiology, has announced that the Second South American Congress of Angiology will be held in Sao Paulo, Brazil, in July 1954. The official subjects of the Congress will be: "Etiopathogenesis of Arteriosclerosis Obliterans," "Medical Treatment of Arteriosclerosis Obliterans," and "Surgical Treatment of Arteriosclerosis Obliterans."

In addition, papers on other aspects of angiology may be sent to the Organization Com-

mittee up to May 1954, accompanied by a summary or abstract of approximately 100 words. Rubens Carlos Mayall, M.D., is President of the Organization Committee. His address is Rua Senador Vergueiro 73, Rio de Janeiro, Brazil.

APPOINTMENT OF ASSISTANT MEDICAL DIRECTOR ANNOUNCED

Charles D. Marple, M.D., Medical Director of the Association, has announced the appointment of Raphael O. Patt, M.D., as an Assistant Medical Director. The staff of the Association's Medical Division now includes two Assistant Medical Directors. Frederick J. Lewy, M.D., has held that position since July 1951.

Dr. Patt was engaged in the private practice of medicine in Johnson City, N. Y., for six and a half years, starting in 1945. During this time he was also associated with the Medical Department of the Endicott Johnson Corporation. Since 1951 Dr. Patt has completed an eight-month postgraduate course in internal medicine at the University of Pennsylvania and a one-year course in cardiology at Harvard University, under Howard B. Sprague, M.D., and Edward F. Bland, M.D.

Born in West Orange, N. J., in 1911, Dr. Patt accompanied his parents to Lithuania in 1922. He received his medical degree at the Medical School of Vytauto Didziojo University in that country in 1938. Returning to the United States in 1940, he served his internship at Fairview Park Hospital in Cleveland and later held a residency in obstetrics at that institution. Dr. Patt has also served residencies in psychiatry at New Jersey State Hospital, Marlboro, N. J., and in medicine at Jennings Memorial Hospital in Detroit.

TELEVISION "PROGRESS REPORT"

Four Boston physicians prominent in activities of the American Heart Association participated recently in the NBC network television program, "The March of Medicine," a joint presentation of the American Medical Association and Smith, Kline & French Laboratories. They were Herrman L. Blumgart,

Howard B. Sprague, Paul D. White and Robert W. Wilkins. The theme of the October 8 telecast was: "Progress Report #1: The Heart." It featured discussion and demonstration of recent advances in the field of coronary artery disease and hypertension.

SEMINARS ON CARDIOVASCULAR PHYSIOLOGY AND HEART DISEASES IN CHILDREN

The St. Francis Sanatorium for Cardiac Children in Roslyn, Long Island, has announced a series of seminars to discuss cardiovascular physiology and treatment of heart diseases in children. The program started in October. Remaining seminars in the series will be held on December 8, January 12, February 9, March 9, April 13, and May 11. A folder describing the series may be requested from the Scientific Committee of the Medical Staff of the Sanatorium.

YOUNGSTOWN RESEARCH GIFT

The Youngstown Area (Ohio) Heart Association has contributed $12,500 to the national research program of the American Heart Association. This sum is in addition to its regular contribution to the national research fund in which all affiliated Heart Associations participate.

MEETINGS

Dec. 1–4: American Medical Association, Seventh Annual Clinical Sessions; Jefferson Hotel and Kiel Auditorium, St. Louis, Mo.

Jan. 4: American Federation for Clinical Research, Eastern Section, Jimmy Fund Building, Children's Medical Center, Boston; Jan. 28: Western Section, University of Oregon Medical School, Portland; Jan. 29: Southern Section, Jung Hotel, New Orleans.

Jan. 6–22: Pan American Medical Association, International Medical Cruise Congress, S.S. Nieuw Amsterdam; Joseph J. Eller, M.D., Executive Director, 745 Fifth Avenue, New York 22.

March 27–28: American Psychosomatic Society, Eleventh Annual Meeting; Jung Hotel, New Orleans; George L. Engel, M.D., Chairman, Program Committee, 551 Madison Avenue, New York 22.

April 1–4: American Heart Association, Thirtieth Annual Meeting; Conrad Hilton Hotel, Chicago.

April 1–2: Assembly of the American Heart Association.

April 3–4: Scientific Sessions of Section on Clinical Cardiology of the Scientific Council, American Heart Association.

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